BONE AND BONES

FUNDAMENTALS OF BONE BIOLOGY

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To the Memory

of

Jakob Erdheim

PREFACE TO SECOND EDITION

Many of the reviews of the first edition of *Bone and Bones* have encouraged our belief in the usefulness of a book which attempts to treat the normal and pathologic behavior of the skeleton on the basis of biologic principles. This belief in the necessity for such a book has been strengthened by the neglect of principles of biology only too apparent in many a recent book or article

In preparing the second edition we have tried to apply the same general principles of biology to a consideration of the many advances which have since been made in our knowledge of the histology and biochemistry of the fascinating tissue we call bone For the first time it seems possible to outline more fully a hypothetical mechanism of bone formation and resorption and to present a basic concept of skeletal growth especially of the growth of the skull

The first part has been enlarged by a discussion of some of the peculiar features of the otic capsule to the second was added a discussion of osteoid osteomas and cementomas, of fibrous dysplasia of bone and of some peculiar genetic disturbances of the skeleton

We know that this book still is not complete and certainly is not free from errors Our aim was and is merely to provide a common basis of discussion for the histologist, biochemist pathologist and clinician.

J P W
H. S

Chicago

PREFACE TO FIRST EDITION

A pathologist and an anatomist, each with a working knowledge in the other's field, have joined forces to write this book. One reason for their co-operation was the peculiar existent dissociation of clinical experimental and pathologic endeavors on one side and biologic thinking on the other. Many papers and books in many special fields of human biology and pathology are characterized by such dissociation, a consequence of the unavoidable and progressive specialization of both practitioners and theorists. Because of the growing restrictions of the special fields, an attempt to summarize and unify the results of the many labors is imperative from time to time. This calls for courage, above all. No single man or working team of two can claim a complete knowledge of the literature in all the special fields which could be included under the heading *Biology of Bone*. And still the task had to be undertaken in order to prevent the experts from becoming people who know more and more about less and less. These experts need the stimulus, and perhaps the irritation, derived from a detached survey of facts and theories which diminishes details but permits a vision of the greater plan.

Frequent use has been made of working hypotheses. Such procedure may be dangerous, but a look on the brighter side is suggested. A working hypothesis is not only an attempt to summarize logically and thus to explain the present knowledge, it is also a plan for further study, an outline of past as well as of future research. That the hypothesis may be proved false does not matter. Science progresses by using the dead and dying ideas of today as stepping stones.

Furthermore the book is an attempt to eliminate the differences between the diverse viewpoints of those who clinically and microscopically, roentgenologically and chemically examine bone and bones and of those who experiment with bone and bones. It tries to bury once and for all the specters of halisteresis or decalcification, interstitial growth of bone, physical plasticity and creeping replacement, which are resurrected again and again by the magic of the imagination.

The book is intended to be a challenge to the research worker, a guide to those who work on bone and on bones in their medical specialty, orthopedists, radiologists, metabolists, dentists, orthodontists, and an aid to the teacher who wants to integrate his particular field into the greater unit of biology.

J P W

Chicago.

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BONE AND BONES

FUNDAMENTALS OF BONE BIOLOGY

INTRODUCTION

Although created and constantly molded by man language and linguistic terms influence man's thinking to an astonishing degree All too often linguistic ambiguities are the cause of unnecessary confusion. It is then that a clarification of terms and their use is imperative.

Dry bones consist of bone only hence the use of the same word *bone* for the tissue *bone* and for the *organ bone* as a unit of the skeleton, which has confused and complicated the understanding of this chapter of biology The pathologist speaks of *bone tumors* and means *tumors of the bones* The anatomist speaks of membranous and endochondral *bone formation* instead of *formation of bones* This leads, in the first case, to the greatest difficulties in establishing a natural classification of the tumors of the skeleton—the bones—and, in the second, to a perpetuation of the idea of two different types or kinds of bone tissue There is only one type of development of bone But there are two types of development of bones.

There is a simple way out of these difficulties leading to great clarity

Bone is a tissue.
Bones are organs.

PART I

NORMAL STRUCTURE AND GROWTH OF BONE AND BONES

CHAPTER 1

BONE TISSUE

STRUCTURAL ELEMENTS OF BONE TISSUE

- Osteocytes
- Intercellular Substance
- Osteoblasts
- Osteoclasts

ARRANGEMENT OF THE ELEMENTS OF BONE TISSUE

- Spongy Bone
- Compact Bone

DEVELOPMENT AND GROWTH OF BONE TISSUE

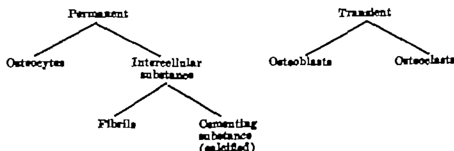
- Formation of Organic Matrix
- Calcification of Matrix
- Immature Bone
- Growth of Bone Tissue
- Replacement of Immature Bone
- Development of Compact Bone
- Regeneration and Reconstruction of Bone
- Cementing Lines

STRUCTURAL ELEMENTS OF BONE TISSUE

As a living tissue, bone consists of two permanent elements specialized cells and their product, the intercellular substance. The cells are known as *osteocytes* The intercellular substance is composed of *fibrils* and a *calcified cementing substance* Two types of cells are observed during active stages of bone destruction or formation only and can, therefore, be termed "transient elements of bone tissue as distinct from its permanent elements. The cells which are active in bone formation are known as *osteoblasts* while those causing resorption of bone are the *osteoclasts*

TABLE I

ELEMENTS OF BONE TISSUE



Osteocytes.—The cells of the mature bone show a uniform and characteristic picture The cell body is shaped somewhat like a plum stone and extends

numerous branching processes in all directions, many of which fuse with similar processes of neighboring cells (Fig 1) Thus, over variably wide areas the osteocytes form a syncytium The cytoplasm of the bone cells is granulated and slightly basophilic it may contain fat droplets which indicate a metabolic activity of the osteocytes. Mitochondria and a Golgi net are present In hematoxylin-eosin preparations the nucleus is darkly stained because of the coarse structure of the chromatin substance Mitosis does not occur in osteocytes.

In dry ground sections, the lacunae which contained the bodies and the canaliculi which contained the processes of the osteocytes are filled with air (Figs. 2 and 3) Because of total reflection of light from a convex surface of air they appear black in transmitted light. This picture induced the first observers to describe these spaces as "bone corpuscles."

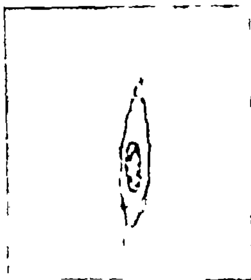


Fig. 1—Osteocyte. Decalcified section through a human mandible Hematoxylin-eosin stain. Longitudinal section (Magnification ×1350)

The peculiar shape of osteocytes and of the cavities in which they are contained causes distinct differences in sections which are cut in different planes. In a longitudinal section the body of an osteocyte appears as an elongated oval whereas a cross section reveals a shorter oval shape Seen from the broad surface or cut parallel to it the osteocyte or the bone lacuna resembles a slightly irregular broad oval the two axes of which are not too different in length A comparison of the shape of osteocytes in any section through bone permits the recognition of the course of the sectioned lamellae

Intercellular Substance.—The intercellular substance* containing the osteocytes in lacunae and their processes in canaliculi appears almost homo-

* Some authors use the terms "ground substance" and "matrix" as synonyms and also as synonymous with the term "intercellular substance." Matrix is, however sometimes understood to mean an early developmental stage of the intercellular substance, while ground substance means to some authors only part of the intercellular substance, namely the cementing substance An agreement with respect to these terms seems highly desirable. To avoid confusion in the following pages, the terms matrix and ground substance will not be used at all in describing the supporting tissues.

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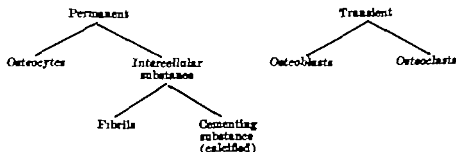
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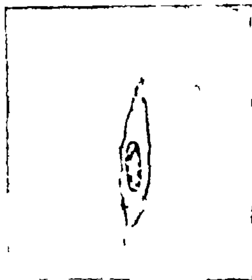


Fig. 1.—Osteocyte. Decalcified section through a human mandible Hematoxylin-eosin stain. Longitudinal section. (Magnification ×1350)

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geneous in ground sections as well as in the decalcified sections stained with hematoxylin and eosin. Special methods, such as silver impregnation reveal fine collagenous fibrils which are arranged in bundles varying in thickness

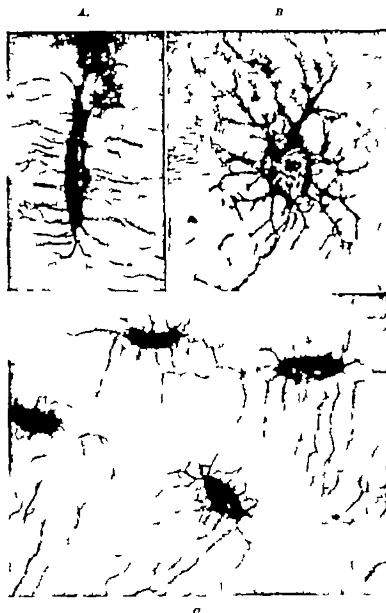


Fig. 2.—Lacunae and canaliculi. Dried ground section of human bone. (Original magnification ×1360 reduced to [illegible])

A. Longitudinal section.

B Surface view Note the cross sections of canaliculi opening on the surface of the section.

C Cross section through lamellae of two Haversian systems Note the looping of the peripheral canaliculi.

from 3 to 5 microns (Fig 4) The invisibility of the fibrils in routine preparations is due to the fact that fibrils and cementing substance have nearly the same refractory index The fibrils are, therefore, referred to as masked.

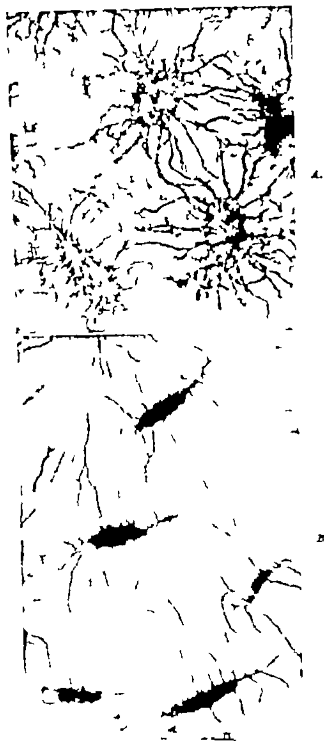


Fig. 3.—Anastomoses between the canaliculi of adjacent lacunae. Dried ground section (Original magnification ×1350 reduced to ¾.)

A Surface view of lacunae.

B Cross section of lacunae of a Haversian system.

The cementing substance consists mainly of polymerized glycoproteins to which the mineral salts, mainly calcium phosphates, are bound. A thin layer of the intercellular substance lining the bony lacunae and canaliculi can be differentiated because of its staining reaction and higher refractory index. In ground sections this area appears as a bright line around the osteocytes and their processes. The lining of lacunae and canaliculi in hematoxylin-eosin-stained sections is darkly stained with hematoxylin (Fig 1) Silver impregnation leaves this part of the intercellular substance entirely unstained (Fig 5) Basophilia is, therefore, combined with argyrophobia.

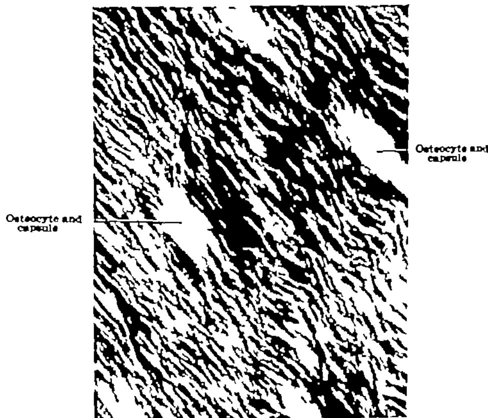


Fig. 4 —Bundles of fibrils in the ground substance. Decalcified section through a human mandible. Silver impregnation. The cells and cementing substance remain unstained. (Original magnification ×1400 reduced to $\frac{5}{8}$)

Silver stains reveal also that the different appearance of the lining of the bone cavities is caused by the lack of fibrils. This layer has a high resistance to alkalies which destroy the other parts of the intercellular substance. It is termed the capsule of the osteocytes.

Osteoblasts.—There is no doubt that the osteoblasts are responsible for the formation and calcification of the intercellular substance of bone tissue. In the formation of new bone the osteoblasts arrange themselves in a continuous layer Their shape varies considerably and there is good evidence for a correlation of the shape and size of the osteoblasts and the rate of bone formation.



Fig. 5.—Nonfibrillar "capsule" of the osteocytes. Decalcified section through the mandible of newborn infant. Hortega silver impregnation. (Original magnification ×1200 reduced (⅘.)

Where bone formation proceeds at a high rate the osteoblasts are of an irregular cuboidal shape measuring 15 to 25 microns in diameter Their spherical nucleus is eccentrically located always near that surface of the cells that is not in contact with the bone (Fig 6) In the basophil cytoplasm, a

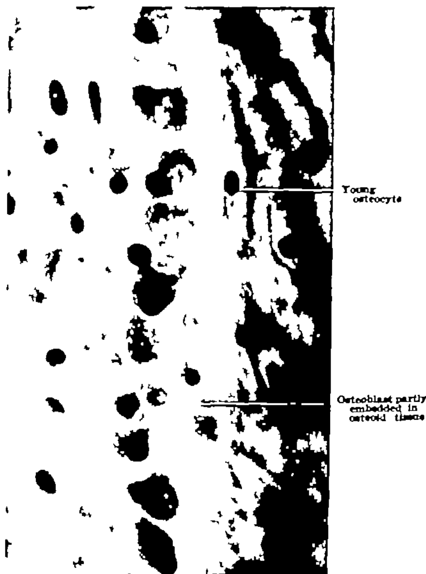


Fig 6—Osteoblasts. Decalcified section of the mandible of a young white rat. Bone of immature coarse fibrillar type. (Magnification ×1240)

Golgi net and mitochondria are found. A vacuole in the neighborhood of the nucleus contains the attraction sphere and the centrioles. Though most descriptions confine themselves to the picture of cuboidal osteoblasts, they are but rarely found in the adult skeleton. Here, where bone formation is a slow process, the osteoblasts are low-cuboidal or squamous in shape In these cells

also the shape of the nucleus is altered correspondingly and it appears much denser than in the large cells typical for the period of rapid growth of the skeleton.

The osteoblasts are united by intercellular bridges. In the course of bone formation some osteoblasts are surrounded by the intercellular substance and thus become osteocytes. The intercellular bridges lengthen considerably during this process, developing into the branching and anastomosing processes of the osteocytes.

Osteoclasts.—The vital changes of bone are caused by an interplay of destruction and formation of bone Bone resorption, which can be observed throughout the growth period of the skeleton is found in the adult body wherever regenerative or reconstructing processes of bone occur Destruction of bone is, therefore an integral part of the biology of bone. Removal of bone always entails simultaneous disappearance of the organic and the inorganic components of the intercellular substance.

The occurrence of decalcification (halisteresis) of the living bone has never been proved and it seems certain that it does not take place. Decalcification would entail a considerable rise in local acidity and there is not the slightest evidence of such a change in the pH of the tissue fluid. It is more probable that the resorption of bone starts with the removal of the organic components of the intercellular substance by a proteolytic action of the osteoclasts The calcium salts, liberated through the removal of the organic parts of the intercellular substance may be made soluble by the action of chelating substances produced by the osteoclasts. If the destruction of bone is rapid the mineral salts are sometimes ingested and carried away by macrophages. Calcium salts have never been found in the osteoclasts but have been shown in macrophages even at some distance from the area of bone resorption. The final changes that make the calcium salts ingested by macrophages available to the organism are as yet unknown.

Occasionally one can observe that osteocytes are incorporated into osteoclasts (Fig 7) In all probability they are then digested by these cells. It has been claimed that osteocytes liberated by the resorption of the intercellular substance may revert to fibroblasts or may differentiate into either osteoblasts or osteoclasts. These claims are not substantiated by good evidence and are highly improbable

The osteoclasts are generally multinucleated giant cells of varying size and shape Their cytoplasm is frequently irregular in outline with branching processes of varying length and often contains vacuoles. Where the osteoclasts are in contact with the bone the protoplasm has sometimes a striated appearance (Fig 8) The acidophilic reaction of the cytoplasm of the osteoclasts is an important diagnostic character The nuclei vary in number in each cell but it has to be stressed that uninuclear osteoclasts do occur The average number of nuclei in an osteoclast varies from 12 to 20 but may rise to 100 The nuclei are poor in chromatin substance and, as a rule contain one or two distinct nucleoli During periods of rapid destruction of bone several osteoclasts may

be found to be connected by cytoplasmic bridges, thus forming a syncytium along or around bone trabeculae The osteoclasts are often found in more or less shallow grooves on the surface of the bone These grooves which look as if they had been hollowed out by the osteoclast, are called Howship s lacunae

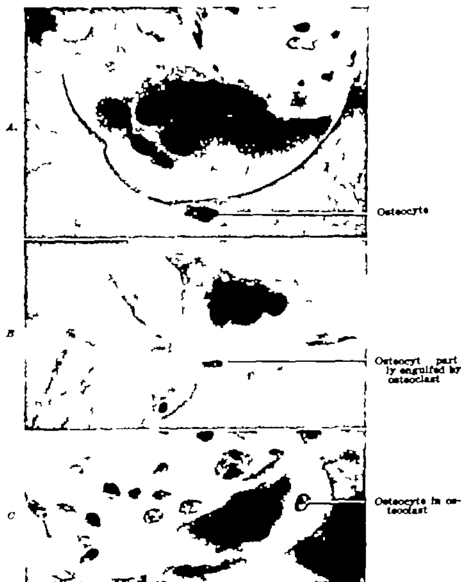


FIG. 7—Fat of osteocytes during osteoclastic resorption of bone. Decalcified section of human bone. Hematoxylin-eosin stain. (Original magnification ×700 reduced to ⅔)
A. The lacuna of an osteocyte is being opened.
B Osteocyte being incorporated into an osteoclast.
C Advanced stage of incorporation of an osteocyte into an osteoclast.

The great size and variable shape of the osteoclasts have caused many misinterpretations of single histologic sections Study of serial sections may for instance reveal that an empty Howship s lacuna is occupied by the cyto-

plasmic part of an osteoclast In other instances enlarged' bone lacunae containing parts of an osteoclast are revealed as tangential sections through the depth of a Howship s lacuna The presence of many nuclei is not a necessary attribute of an osteoclast Small cells with one or two nuclei may be diagnosed as osteoclasts by their relation to bone tissue and by their acidophilic cytoplasm.

The assumption of a humoral as against a cellular destruction of bone is also disproved by the obvious fact of strictest localization of bone resorption to the area covered by osteoclasts. Sometimes bone apposition occurs in close approximation to an area of bone resorption (Fig 9)



Fig. 8.—Osteoclast with striated border in a Howship lacuna. Decalcified section of human bone. Hematoxylin-eosin stain. (Magnification ×700.)

Osteoblasts as well as osteoclasts, develop by differentiation from cells of the loose connective tissue Maximow s undifferentiated mesenchymal cells, or reticular cells. The claim that osteoblasts occasionally originate from liberated osteocytes and that osteoclasts arise by fusion of osteocytes is unsubstantiated

Though self-evident the fact has often been forgotten that resorption of bone is always accompanied by proliferation of the adjacent connective tissue This includes not only the mitotic division of cells and the elaboration of intercellular substance but also the formation of new capillaries. Observations of this kind have led to a description of bone destruction by capillary erosion or by invasion of connective tissue.

The conditions which lead to the differentiation of osteoclasts are still under discussion The first possibility is that ageing or necrosis of bone mani

fested by ageing or necrosis of osteocytes, leads to a chemical change of the intercellular substance At the surface of the bone cells of the adjacent connective tissue would be stimulated by these chemical changes to *differentiate* into osteoclasts.



Fig. 9 —Osteoclast and osteoblasts in close proximity to each other to show the minute localization of destruction and formation of bone.

A second possibility is that the stimulus for the differentiation of osteoclasts is an increase of pressure in the tissue adjacent to the bone According to this theory, the pressure would be directly responsible for the initiation of osteoclasis. It is, however more likely that pressure leads to osteoclastic resorption of bone by primarily causing a circulatory disturbance in the nutritive tissue of bone for instance in the periosteum or bone marrow

The third possibility is the direct action of elements of the blood or tissue fluid which induces the differentiation of osteoclasts. Decrease in the calcium blood level was mentioned as a stimulus to bone resorption The fall of the calcium blood level acts, however not directly but by stimulation of the parathyroid gland

Attempts have been made to elevate one of the mentioned factors to rank of the only cause of bone resorption Decrease of the vitality of osteocytes or their necrosis has been suggested as the direct stimulus to dif entiation of osteoclasts I ressure or a change in the blood chemistry is posed to act indirectly by causing primarily more or less severe damage to osteocytes or by effecting chemical changes of the intercellular substance

Increase of pressure as the universal cause for bone resorption is widely discussed Osteoporosis in disuse atrophy is then explained as result of a primary stasis of the circulation in the bone marrow and per teum, leading to an edema and thus to a rise of the tissue pressure.

It is, as yet impossible to reach a decision in this discussion mainly cause of an inability to observe the minute changes in the chemical physi or morphologic behavior of the osteocytes and the intercellular substance. I believed however that changes in the chemistry of bone play the most import role as stimulus for the differentiation of osteoclasts. One could divide tl changes into intrinsic and extrinsic changes. The intrinsic changes wo depend upon changes in the vitality of the osteocytes Extrinsic char would depend upon the influence of blood and lymph directly on the in cellular substance of the bone

ARRANGEMENT OF THE ELEMENTS OF BONE TISSUE

Mature bone is lamellated, that is, it is laid down in thin layers of in cellular substance 4 to 12 μ thick, with the osteocytes spread out in the plan the lamella The osteocytes are found in and between the lamellae. S of their processes perforate a lamella to communicate with those of the in the adjacent lamella as well as those farther removed The fibrils in matrix are arranged in different directions in adjacent lamellae This o *permits differentiation of the lamellae in sections. If the fibrils in two la*lae are at right angles to each other, one lamella may appear striped the ot stippled. The change in the direction of the fibrils is, in fact the reason mature bone appears to be lamellated Such an arrangement of fibrils incre the resistance of bone to mechanical forces, especially to shearing forces. T is only one localization in which bone is almost exclusively under tensile for namely in the innermost layer of the dental alveoli to which the suspen fibers of the periodontal membrane are attached. Here the direction of fibrils is not subject to a regular change from layer to layer and thus lame of the bone are indistinguishable The shape and arrangement of lamellae markedly different in the two types of bone, which can be distinguished ma scopically as spongy or cancellous bone and compact bone

Spongy Bone.—Spongy bone consists of bars, plates, or tubules of b of varying thickness and length and joined to a three-dimensional netw (Fig 10) The spaces between the trabeculae communicate throughout

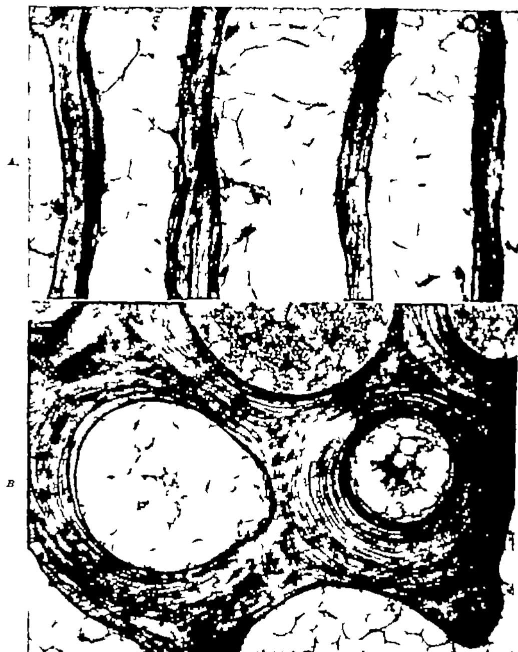


Fig 10.—Two types of spongy bone. Decalcified sections. Hematoxylin-eosin stain. (Original magnification ×100 reduced to ⅘)

A. Human jaw laminar spongiosa.

B Human rib tubula spongiosa

Compact Bone.—In the compact bone most lamellae are arranged in cylindrical systems (Fig 11) Each system consists of a varying number of concentric lamellae, grouped around a narrow axial canal a marrow canal which contains blood vessels (see page 53) and a small amount of loose connective tissue (Fig 12) A system of these concentric lamellae is called a Haversian system, with its Haversian lamellae around the Haversian canal. The osteocytes of the

Haversian system are arranged with their long axis parallel to the long axis of the system and their broad surface parallel to the lamellae (Figs. 11 to 14) The canaliculi of the innermost lamella open into the Haversian canal Thus processes of the osteocytes are in contact or continuity with the connective tissue cells of the Haversian marrow canal to allow the circulation of tissue fluid through the syncytium of the osteocytes and into the intercellular substance The canaliculi of the lacunae in the outermost lamellae communicate

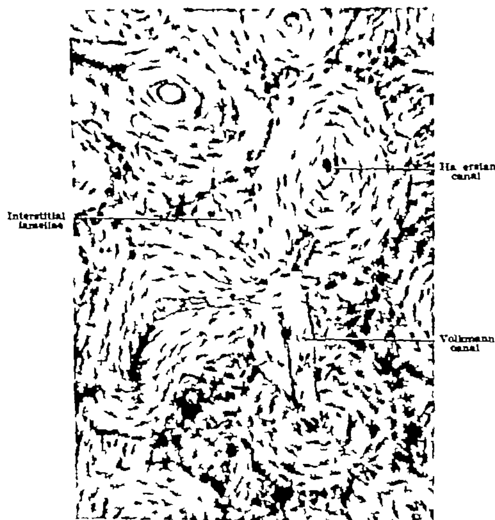


Fig. 11.—Haversian systems and interstitial lamellae in cross section. Dried ground section through human bone. (Original magnification ×180 reduced to ⅘)

but rarely with those of an adjacent Haversian system. In most cases, they form short loops reaching back into the lacuna from which they arise (Fig 2 C)

The lamellae of a Haversian system from five to twenty in number are easily distinguished by the different direction of their fibrils which run longi



Fig. 12.—Cross section through a Haversian system under high magnification. Dried ground section through human bone. (Magnification ×260.)

tudinally in one lamella circularly in the next and so on (Figs. 15 and 16) The bundles of fibrils in each lamella cross each other at acute angles but the general flow of the fibrils is maintained (Fig 4)

The Haversian blood vessels are linked to each other by short cross connections *which perforate the lamellae of two adjacent systems. The canals* in which these blood vessels are found are called Volkmann's canals (Fig 11)

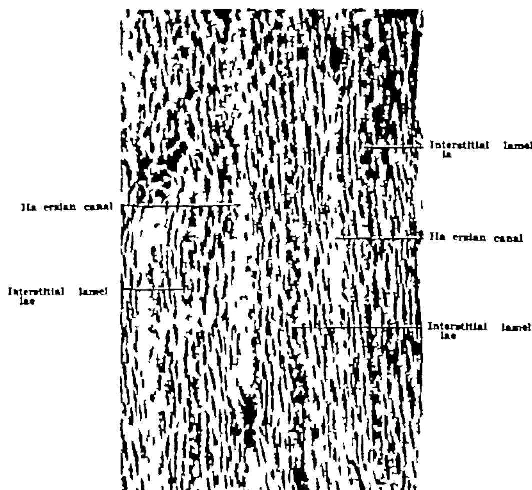


Fig. 11.—Longitudinal section through Haversian systems Dried ground section through human bone (Original magnification ×120 reduced 1 5)

Such canals also perforate the outer or inner layers of the compact bone to allow communication of the Haversian vessels with the vessels of the periosteum or the bone *marrow (Figs. 17 18 and 43)*

Between the densely packed Haversian systems are irregular spaces which are occupied by irregularly arranged lamellae, the interstitial lamellae (Figs. 17 and 19) Their origin from partly destroyed Haversian systems, or remnants of circumferential lamellae, will be discussed with the growth and reconstruction of bone.



Fig. 14.—High magnification of longitudinal ground section through Haversian lamellae of human bone. (Magnification ×400.)

Osteocyt and capsul

Osteocyt and capsul

ocyte nd apsule

A *B*

Fig. 15.—Alternating course of fibrils in adjacent lamellae of the intercellular substance. Decalcified section through a human mandible. Silver impregnation. (Original magnification ×1600 reduced to ⅘.)

A Part of a Haversian system in cross section. Striped and stippled lamellae.

B Part of a Haversian system in longitudinal section.

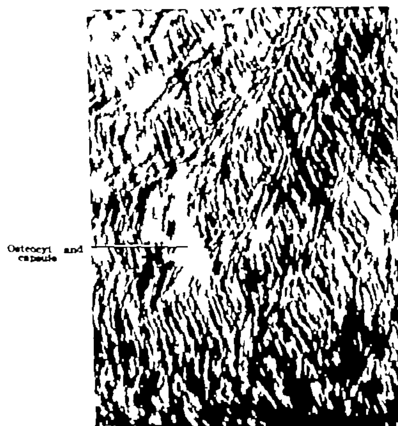


Fig. 16.—Surface view of two flat lamella showing the crossing of the fibrils in the intercellular substance. Decalcified section of a human mandible. Silver impregnation. (Original magnification ×1600 reduced to ⅘.)



Fig. 17.—Compacta of a long bone in cross section. Decalcified femur of an adult rabbit. Hematoxylin-eosin stain. (Magnification ×115.)

The growth of a long bone in thickness, by means of the apposition of new lamellae upon the entire surface of the bone accounts for the development of lamellae circling the entire shaft of a bone. These lamellae are known as the outer basic or circumferential lamellae. *After completion of growth, similar* lamellae are laid down on the inner surface (the inner basic lamellae) of the compact bone lining the marrow cavity (Figs. 17 18 and 19)



FIG. 18.—Detail of section shown in Fig 17 under high magnification. (*Original magnification* ×400 reduced to ¾)

A. Outer circumferential lamella ; perforating Volkmann's canal.
B. Inner circumferential lamellae perforating Volkmann's canal.

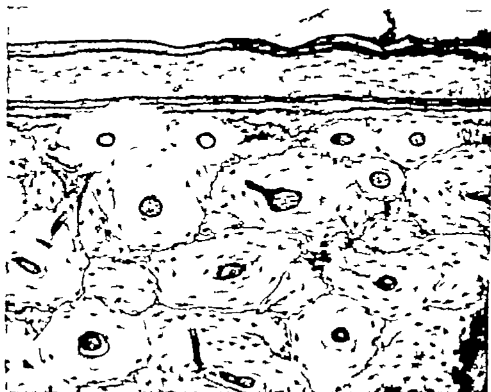


FIG. 19—Compact bone of the mandible of a dog. Note the Haversian, interstitial, and circumferential lamellae. (Original magnification ×140 reduced to ¾.)

DEVELOPMENT AND GROWTH OF BONE TISSUE

The terms endochondral and membranous or intramembranous bone formation have often been misinterpreted as if there were at least two types of osteogenesis. In reality these terms refer to the gross development of bones as organs of the skeleton. Osteogenesis, on the other hand, that is, the formation of bone tissue occurs always and everywhere in the same way Whether we deal with the first appearance of bone spicules in the mesenchyme of the embryo at the vault of the skull or with the appearance of bone trabeculae around a cartilaginous model of a bone whether we deal with the development of bone inside the destroyed cartilaginous model or with the appositional growth of spongy or compact bone whether we observe the healing of fractures or the ectopic or neoplastic formation of bone the process of osteogenesis is in principle identical The mother tissue is always loose connective tissue

Though many details of the complicated process of osteogenesis are still controversial a bame though hypothetical picture has emerged. It seems to be justified to divide the histogenesis of mature bone into three overlapping phases. In the first phase the osteoblasts produce a homogenous, organic intercellular substance This substance is reorganized in the second phase while the mineralization or calcification occurs in a third phase Second and third phases seem to proceed, at least in part simultaneously

The first sign of bone formation is the appearance of a *hyalinized, homogenous* intercellular substance either around cells of the embryonic mesenchyme (Figs. 20, 21) or on surfaces of calcified cartilage or bone. The fibrils or fibers present before bone formation starts *seem to disappear while the cementing* substance, originally semifluid in character, assumes a much higher consistency. The collagen molecules of the depolymerized fibrils and the highly polymerized glycoproteins of the cementing or ground substance *form at this time a homogenous* substance slightly eosinophil that resembles hyaline. This substance may be termed primary osteoid tissue.



Fig. 18.—Early stage in the development of bone. Mandible of a human embryo 20 mm. long. Mallory Azan stain. Irregular network *of hyalinized* mesenchyme encapsulating groups of cells. (Original magnification ×1350, reduced to ⅔.) (Specimen courtesy Dr. P. Gruenwald.)

The next phase of osteogenesis leads to the formation of a fibrillar calcifiable intercellular substance, the secondary osteoid tissue. The changes involved in the second phase can be visualized as a reconstitution of the molecules of collagen into the osseous fibrils that as a rule have a *direction entirely different from that of the fibrils* of the connective tissue in which osteogenesis occurs. If this can be termed a *polymerization of collagen* leading to a chain formation and a cross bondage of collagens, the other change is in

all probability a depolymerization of the glycoproteins. During this process unsaturated side chains may be exposed that combine with the mineral salts in the next phase of osteogenesis. The details of the formation of the apatite crystals is still a matter of conjecture.

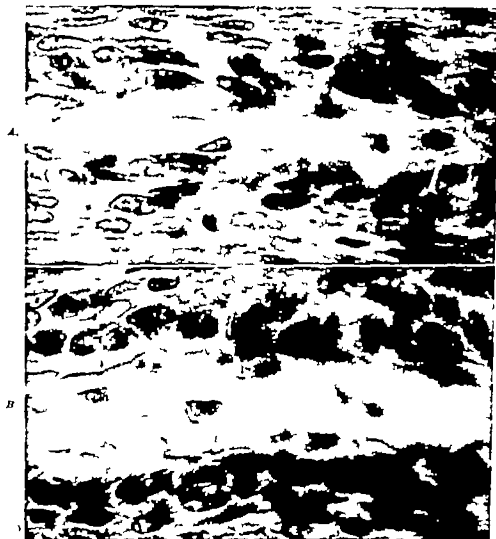


Fig. 21.—Two stages in the development of primitive bone. Parietal region of new born rat. Hematoxylin-eosin stain. (Original magnification ×1350 reduced to ¾.) (Specimens courtesy Dr. Skullen.)

A Hyalinization of the intercellular substance in the embryonic connective tissue.

B Advanced stage. Differentiation of typical osteoblasts lining the bone spicule.

It has been apparent for some time that calcification of osteoid tissue cannot be considered as a mere addition of mineral salts to the osteoid tissue by a process of precipitation. Two observations were responsible for the assumption that a change of the organic component of osteoid tissue is essential during its calcification. (1) In decalcified sections, stained with hematoxylin-eosin, the intercellular substance of fully developed bone stains differently from the not yet calcified osteoid tissue; the former stains a deep

purple while the latter remains either unstained or light pink. (2) Osteoid tissue is highly resistant to resorption. Since in the process of resorption of bone the destruction of the organic components by proteolytic enzymes plays a most important role, the different behavior of osteoid tissue and bone must be caused by a difference in the organic component

The changes of the osteoid tissue as outlined in this working hypothesis, explain not only the differences in staining reaction of osteoid tissue and the organic component of decalcified bone but would also explain why the highly polymerized glycoproteins of osteoid tissue lose their resistance to proteolytic enzymes after their depolymerization and subsequent calcification.

It appears now that calcification is not necessarily dependent upon a local concentration of calcium and phosphorus ions, but may be the direct consequence of the changes of the glycoproteins of the osteoid tissue. This hypothesis is supported by the observation of calcification of cartilage preceding and preparing its resorption. Here calcification is of no functional significance and, evidently the unavoidable consequence of a change (depolymerization) of the organic intercellular substance (see page 59)

All the changes sketched in the previous paragraphs must be visualized as being dependent on the enzymatic activity of the osteoblasts What the specific enzymes are and what specific role they play is still a matter of conjecture At least two enzymes have been localized by histochemical methods in osteoblasts, namely alkaline phosphatase and phosphorylase both seem to be active during osteogenesis.

The chemical and submicroscopic structure of the mineral salts in bone tissue is still controversial. However it seems to be certain that the calcium phosphates are present in the form of hexagonal apatite crystals, either hydroxylapatite or tricalcium phosphate hydrate The other mineral components, carbonate, fluor magnesium, and others seem not to exist in chemical but rather physical relation to the apatites, possibly adsorbed to free or trapped surfaces. It is therefore not yet clear how many of these adsorbed ions are available for ionic exchange or for withdrawal from bone tissue.

Immature Bone.—The bone formed in the early stages of bone development is markedly different in its structure and in details of histogenesis from that of mature bone The differences lie in the intercellular substance as well as in the osteocytes. The bundles of fibrils in the matrix of immature bone are coarse and irregularly arranged. The osteocytes are numerous, but irregular in shape and arrangement and have only a few processes. This immature primitive or coarse fibrillar bone is always arranged in trabeculae and is, therefore always spongy bone (Figs. 22 and 23)

The larger size and the greater number of the osteocytes in the immature bone are the reason that a unit volume of immature bone contains less intercellular substance than the same volume of mature bone In addition, the cementing substance is still more reduced in comparison to mature bone by the coarseness of the fibrils of the immature bone Therefore a unit volume of immature bone contains considerably less of the calcifiable cementing sub-

stance than mature bone Since the radiopacity of bone tissue depends on the number of mineral molecules in a given volume, immature bone is far less radiopaque than mature bone



Fig. 22.—Immature coarse fibrillar bone Decalcified section f distal end of shaft of femur Child fou months old. (Hematoxylin-eosin stain. (Magnification ×160)

In many instances a type of bone tissue can be observed that is somewhat intermediary between immature and mature lamellated bone This type of bone is characterized by a fairly regular arrangement of typically shaped osteocytes. The number of bone cells compared to that of immature bone is



Fig. 23.—High magnification of immature bone. Decalcified section of the mandible of a human infant. (Original magnification X650 reduced to [illegible].)

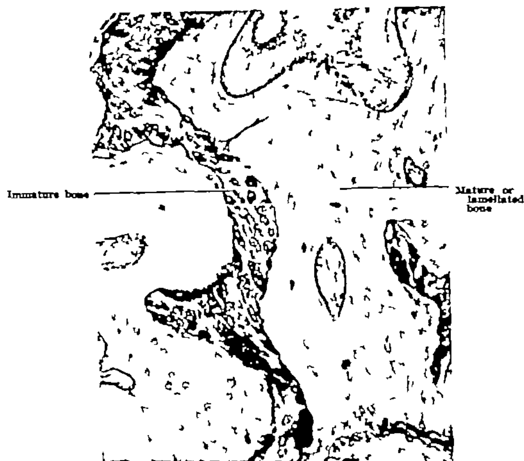


Fig. 24.—Replacement of immature bone by lamellated mature bone. Decalcified section of the mandible of a newborn infant. A narrow trabecula of primitive bone temporarily escaped resorption. The superimposed lamellated bone separated from the immature bone by a *reversal line*. *Note the dark staining* of the immature bone. Hematoxylin-eosin stain. (Original magnification X160 reduced to [illegible].)

also greatly reduced. The fibrils of this intermediary type of bone are thin but are still irregularly arranged. Especially the alternating direction of the fibrils in adjacent layers of bone, and therefore a clear lamellation, is still lacking.

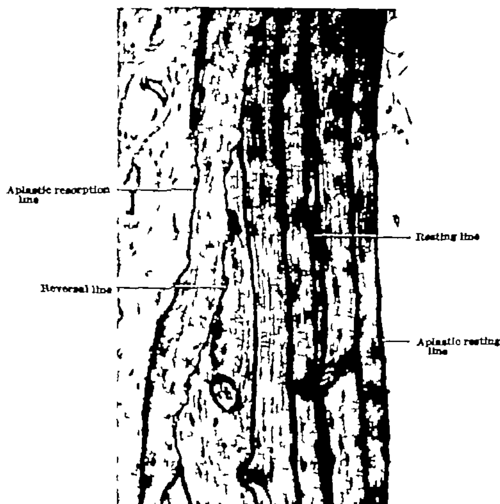


Fig. 25A.—Cementing lines in a bony plate of the mandibular alveolar process. Decalcified section. Hematoxylin-eosin stain. Note the smooth resting lines, the scalloped reversal lines, and the aplastic lines on the surface of the bone. (Original magnification ×210 reduced to ⅘.)

In the histogenesis of immature bone the changes leading to a rearrangement of the collagenous fibrils in mature bone seemingly do not occur. Instead, the collagenous fibers of the connective tissue are without change, embedded in the osteoid cementing substance.

Growth of Bone Tissue.—Bone tissue with its unyielding mineralized intercellular substance is, of course, incapable of expansive or interstitial growth. It was one of the most important advancements of bone biology when it could be demonstrated that bone growth is always appositional or additive. This fact can also be expressed by the statement that bone tissue can grow only on surfaces that are in contact with loose or reticular connective tissue. Only cells of these

tissues can differentiate into osteoblasts that are capable of producing a new layer of bone upon the old. It is both interesting and discouraging that the concept of interstitial growth of bone long since disproved and discarded is still exhumed from time to time by some writers.

Replacement of Immature Bone.—While the immature coarse fibrillar bone is still growing by apposition, its resorption and replacement by mature lamellated bone can be observed (Fig 24) The replacement follows as a distinct second phase after osteoclastic resorption. The assumption of a 'creeping replacement' (in the sense that newly formed bone is in some way responsible for the removal of the old) is based on a misinterpretation of histologic findings.

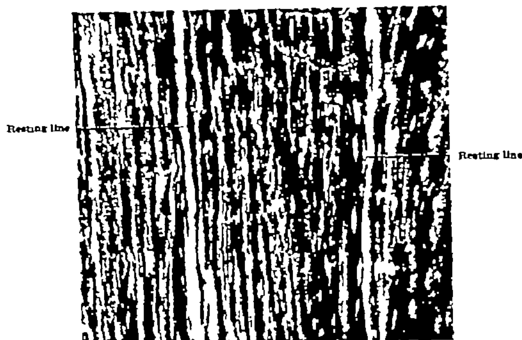


Fig. 24.—Resting lines in a silver impregnated section of a human mandible. The resting lines remain unstained. (Original magnification ×220 reduced to [illegible].)

The replacement of coarse fibrillar bone by lamellated bone during development of the skeleton in the embryo and in early postnatal life seems to be a recapitulation of a phylogenetic process. In the evolution of the vertebrates, the coarse fibrillar bone is the first to develop and only the mammals elaborate lamellated bone.

The gradual replacement of immature by intermediary and finally by mature bone may explain often quoted results of chemical analyses of bone tissue of bones of different age A volume of immature bone contains as was mentioned before less mineral salts than an equal volume of mature bone The increase in mineral content observed during maturation of the skeleton, therefore has to be interpreted as a sign of progressive replacement of immature by mature bone and not of a progressive mineralization of bone tissue with increasing age.

Development of Compact Bone.—Bone develops everywhere primarily as spongy bone. The development of compact bone as it first appears, is a simple phenomenon. The primary spongy bone consists of rather evenly distributed, short, connected trabeculae which bound small polyhedral marrow spaces with centrally located blood vessels. Apposition of concentric lamellae upon *the walls of the marrow spaces reduces the space to such an extent that, finally* only a small canal around the blood vessels remains. Thus a primary Haversian system develops with its Haversian canal and Haversian vessels.

Regeneration and Reconstruction of Bone.—Bone tissue is in continuous flux throughout life. According to the change in the mechanical requirements of the skeleton an internal reconstruction of bone tissue takes place. But aside from these changes which safeguard the close interrelation between function and structure of bones, the nature of the bone tissue itself causes continual changes. Osteocytes, the metabolic activity of which is essential to the normal function of bone tissue have a limited life span but cannot be regenerated by mitotic division as are other cells in the animal body. Therefore, parts of bone with osteocytes nearing or at the end of their life span have to be removed and replaced by new bone with young and vital osteocytes. This regenerative reconstruction of bone is again the result of an interplay of the destroying activity of osteoclasts and the formative capacity of osteoblasts.

During the period of skeletal growth, formation of new bone outweighs its resorption. In the adult the two processes are in balance. In senility however regenerative apposition may lag behind resorptive destruction of bone. The result is the well known senile osteoporosis.

Cementing Lines.—A free and inactive surface of bone shows a peculiar staining reaction (Fig 25*A*). The surface layer becomes increasingly basophilic and can be seen in a section stained with hematoxylin and eosin as a dark blue line aplastic line or limiting membrane. If, after some time, new bone is laid *down upon this surface, its layers are separated from* the old bone by a dark blue cementing line which is now called resting line. It is straight or evenly curved.

If bone tissue is resorbed and resorption ceases for a time, the resorbed surface shows the same reaction as previously described, that is, the appearance of an aplastic line. New bone apposed upon the resorbed surface is separated *from the old* by a *cementing line* which is called a reversal line (Fig 25*A*). It is scalloped with its concavities corresponding to the former Howship's lacunae. The convexities of the scalloped reversal line face the old bone.

In silver impregnated sections the cementing lines remain entirely unstained (Fig 25*B*). Their strong basophilia is matched by complete argyrophobia. The lack of stainability in silver impregnation proves that these lines do not contain any *fibrils. They may consist of cementing substance only* which shows the same staining reactions as the cementing lines.

The presence of resting and reversal lines in a section of bone permits reconstruction of the history of the area of bone in much the same way that the lines of sedimentation and erosion help a geologist to study the history of an area.

CHAPTER II

BONES

STRUCTURAL ELEMENTS OF THE SKELETON

A bone, as an element of the skeleton, consists of different tissues. In the simplest case (for example lacrimal bone) the bone is a plate of compact bone enveloped by a differentiated layer of dense connective tissue, the periosteum.

Most bones, however consist of compact and spongy bone that includes small or large cavities, lined by endosteum and filled with bone marrow In addition, most bones of the skeleton have a covering of hyaline cartilage on some

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The periosteum consists of two layers the outer layer, which is rich in blood vessels and nerves showing a dense arrangement of collagenous fibers (Fig 26) and the inner layer (cambium layer), in which the fibers are loosely arranged, the cells are numerous, and blood vessels are relatively sparse. As long as the bone grows at a periosteal surface a more or less continuous layer of osteoblasts lines the bony surface.

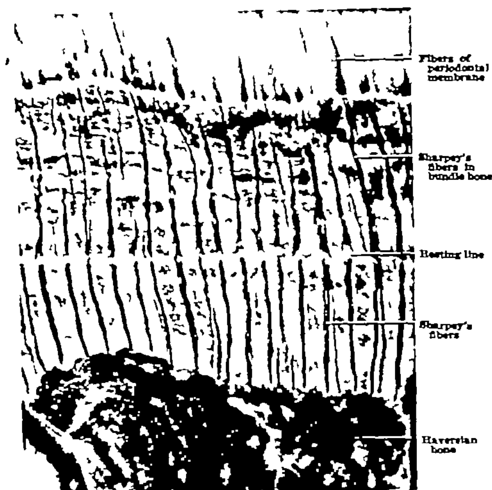


Fig. 27—Alveolar bone in silver impregnation. Note Sharpey's fibers which seem to be interrupted at a resting line. Note, furthermore, the difference between Haversian bone which is rich in fibrils, and the bundle bone, which is poor in fibrils. (Magnification ×130)

Sharpey's Fibers.—A connection of the periosteum with the bone is established by bundles of collagenous fibers of the periosteum which are partly embedded in the outer layer of the bone itself In areas where no muscles, tendons, or ligaments are attached to the bone the fibers generally enter the bone at right angles to its surface The fibers of tendons or ligaments in areas of attachment continue in their course into the bone These fibers embedded in the bone are known as Sharpey's fibers (Fig. 27) They do not calcify as a rule and in dry ground sections of the bone the spaces in which they were contained are visible as straight canaliculi. Areas of bone containing a great number of Sharpey's fibers present a characteristic picture and are termed

bundle bone. Bone in which Sharpey's fibers are anchored may be of the coarse fibrillar type in young individuals or the mature type in the adult. The term bundle bone in the adult does, however indicate a separate type of bone that is lacking the lamellation of the typical mature bone tissue

A





B

Fig. 28.—Sharpey fibers. Decalcified sections of a human lower jaw. Silver impregnation. (Original magnification ×1600 reduced to ¾.)

A Longitudinal section through Sharpey's fibers, the continuation of principal fibers of the periodontal membrane into the bone. Not the cross sections of the fibrils of the bone between the bundles of Sharpey' fibers.

B Cross section through bundles of Sharpey's fibers in the alveolar bone. Again compare Sharpey's fibers with the fibrils of the bone.

The main difference which can be ascertained between bundle bone and simple mature bone is a scarcity of fibrils in the bundle bone (Fig 27) The fibrils are always arranged at right angles to the Sharpey's fibers that is, they run approximately parallel to the surface of the bundle bone (Fig 28) The reduced number of fibrils in bundle bone is especially clear in the alveolar bone, which serves as an attachment of the teeth In sections impregnated with silver the bundle bone is much more lightly stained than the simple lamellated bone because of the argyrophobia of the cementing substance between the fibrils, the amount of which is in inverse proportion to the number of argyrophil collagenous fibrils. In addition there is no regular change in the direction of the fibrils from one layer to the other and, therefore no arrangement of the bone in well-distinguishable lamellae A given volume of bundle bone, therefore, contains a greater amount of cementing substance than lamellated bone. Thus there is in bundle bone also a greater amount of bone salts per unit volume and this in turn explains the higher radiopacity of bundle. The greater density of this bone in oral roentgenograms has been noted and for this reason the bone immediately surrounding the tooth has been called lamina dura

A closer examination of the connection between the fiber bundles outside and inside the bone reveals a typical shrinking and an increased density and stainability of the embedded part of the fibers (Fig 28 *A*) At the point of entrance into the bone there is, moreover an area of intense staining It looks as if a fairly loose arrangement of fibers were tied in a knot where the fibers enter the bone, to continue as a tightly wound rope in the bone itself

Nerves.—The nerves of the periosteum are in part, somatic afferent nerves, a fact which accounts for the high sensitivity of the periosteum. Little is known of the sensory nerve endings beyond the fact that small Vater Pacini corpuscles sometimes are found Sensory nerves seem to enter the marrow following the nutrient arteries. Sympathetic vasomotor nerves follow *the blood vessels, the nutrient arteries as well as those entering the compact* bone through Volkmann's canals. These nerves end on the smooth muscle fibers of the blood vessels.

Bone Marrow—In the fetus and the infant the large marrow space in the shaft of long bones and the small communicating marrow spaces in the spongy bone are filled with red or hematopoietic bone marrow (Fig 29) From the sixth year of life the red marrow is gradually replaced by yellow or fatty bone marrow in the shafts of long bones. Such replacement begins in the bones of the leg (tibia and fibula) and occurs later in the femur in the forearm (radius and ulna) and lastly in the humerus. The marrow in most epiphyses of the long bones likewise changes gradually into fatty marrow so that, in the adult, hematopoiesis proceeds only in the marrow of the following bones flat bones of the skull vertebrae ribs and sternum.

The red bone marrow consists of reticular tissue, the meshes of which are filled with cells representing all the different stages of developing erythrocytes and granulocytes. The blood forming elements disappear during formation of the fatty bone marrow and most reticular cells change into adipose cells. These dominate the picture (Fig 29) The cavities *of the marrow are lined with delicate membrane of connective tissue* the so-called endosteum

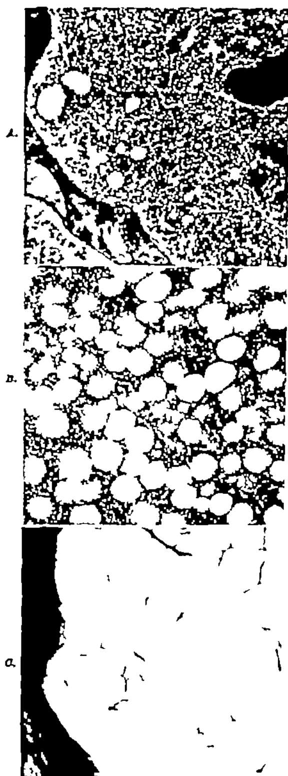


Fig. 29.—Bone marrow. Decalcified section of human bone. Hematoxylin-eosin stain. (Original magnification ×120 reduced to ⅘.)
A. Cellular marrow.
B. Mixed type.
C. Fatty marrow.

Blood Supply of Bones.—The blood supply of bone tissue depends on its arrangement as spongy or compact bone. The blood supply of spongy bone is represented by the blood vessels of the marrow spaces which are generally about equally distant from the surrounding bone trabeculae. In the compact bone the blood vessels occupy the network of the longitudinal Haversian and the connecting Volkmann's canals. The blood vessels in the canals are in communication with those in the periosteum and the marrow.

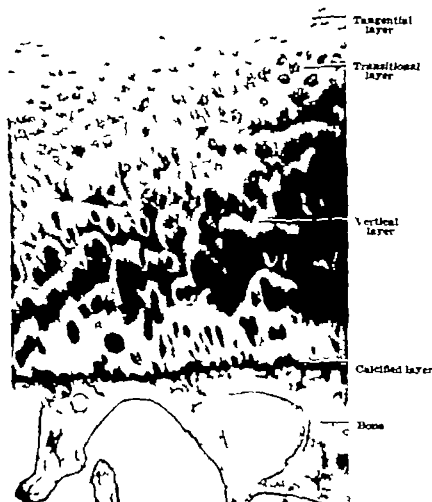


Fig. 18.—Articular cartilage. Decalcified section through the head of a human femur. Hematoxylin-eosin stain. Note the deepest calcified layer of the cartilage in contact with the terminal plate of the epiphyseal bone. (Original magnification ×85, reduced to ⅘.)

Most of the blood vessels inside the compact bone are capillaries. Often two blood vessels are found in one Haversian canal, one of which is a narrow arterial capillary and the other a wider venous capillary. Volkmann's canals contain not only the transverse links of the capillary network, but also arterioles and venules for the connection of the periosteal with the medullary blood vessels of the bone.

The blood supply of a bone is derived principally from two sources. Smaller or larger arteries enter the bone by perforating the compact outer layer and ramify in the bone marrow These arteries are destined for the bone marrow itself and the spongy bone. The second group of arteries supply primarily the compact bone. These arteries are derived from the periosteal network and enter the bone as arterioles or prearterioles in the numerous Volkmann's canals which open at the outer surface. These two systems of the blood supply of a bone are, of course not independent of each other but communicate through numerous, though generally small anastomoses. An exception to this rule exists only in those endochrondral bones which develop from more than one center of ossification and then only during the period in which the bony parts are separated by cartilage.

The degree to which each of the two arterial systems participates in the supply of a bone depends on the structure of this bone Of special significance is the proportion of compact to spongy bone, the presence or absence of a large marrow cavity and the relation of the attachment of an articular capsule to the articulating ends of a bone

The veins of a bone follow the arteries The veins start with extremely wide venous capillaries into which the arterial capillaries open abruptly Inside the bone the veins do not possess valves. Valves are, however found at the point where the larger veins emerge from the bone

The blood supply of long bones and its changes during growth deserve special attention, especially in view of the importance of the circulation to the development of inflammatory and necrotic foci and metastatic tumors. As long as the diaphysis is separated from the epiphyses by cartilaginous discs, the arterial supply of each part of a long bone is independent. The shaft is supplied from three sources, the most important of which is the nutrient artery It is single in the long bones with the exception of the femur into which two nutrient arteries enter The nutrient artery perforates the compact layer of the bone in an oblique course and, in the marrow cavity splits into a descending and ascending branch. After supplying the marrow the nutrient artery sends terminal branches into the metaphyses where they anastomose with metaphyseal arteries. These small arteries are derived from the arteries of muscles and ligaments and enter the metaphysis around its circumference. The metaphyseal arteries are in part, anatomic and, in part, functional end arteries. The metaphyseal capillary network ends toward the epiphyseal cartilage in long hairpin-shaped loops. In addition to nutrient and metaphyseal arteries, the compact cortical layer of the shaft receives numerous small periosteal arteries which enter the Volkmann canals. These are mainly destined for the compact bone but anastomose with the arteries of the metaphysis.

The arteries of the epiphysis originate from the capsular arteries. They form a rather dense network in the epiphysis The course of the capsular arteries from their contact with the bone until they reach the epiphysis itself depends on the relation of the line of capsular attachment to the epiphyseal line. The arteries which supply the head of the femur are especially exposed to danger during their extended course along the neck (Fig. 226)

Anastomoses between metaphyseal and epiphyseal arteries have been claimed repeatedly Branches which perforate the epiphyseal cartilage are however to be considered as exceptions.

After the disappearance of the epiphyseal cartilage the connections between diaphyseal and epiphyseal arteries are numerous, but the anastomosing branches are small With progressing age the nutrient arteries become relatively smaller due to the replacement of the hematopoietic red marrow by fatty yellow marrow

Articular Cartilage.—The articular surfaces of most bones are covered by hyaline cartilage The thickness of the articular cartilage varies considerably In small articulation the cartilage is from 0.2 to 0.5 mm. in larger joints the thickness increases to from 2 to 3 mm. to reach a thickness of 4 mm. in the knee joint.

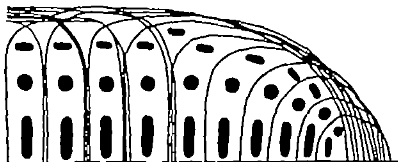


Fig. 31.—Diagram of the arrangement of cartilage territories and fibrils in the central and marginal zones of an articular cartilage. (After Benninghoff.)

In joints which have to withstand considerable pressure the articular cartilage has a characteristic structure (Fig 30) The surface layer is under tensile stress because of the gliding movement of one articular surface on the other This layer contains small flat chondrocytes The fibrils of the hyaline intercellular substance are generally parallel to the surface The cells are large in the deeper layers. They form distinct groups and the fibrils run vertically to the articular surface. Seemingly as an adaptation of pressure the intercellular substance is differentiated into globes of high basophilia surrounding a smaller or larger group of cells. These territories are separated from each other by the lighter-stained interterritorial substance

Superficial tangential and deeper radial zones are connected by a transitional zone in which the flat and small cells of the surface gradually enlarge and group together to form the territories of the deeper layer The cells also change their position. In the superficial or tangential layer their long axis is parallel to the surface. In the transitional zone it is more and more obliquely arranged to be at a right angle to the surface in the deep layers.

The radial fibrils of the deep layer and the tangential fibrils of the surface layer seem to be parts of one system of curved fibrils which ascend in a radial direction through the deep layers and curve in the transitional zone to reach a tangential course in the superficial layers (Fig 31) Out of the superficial zone the fibrils bend again after a shorter or longer course into the depth to end as radial fibrils.

It is interesting that the dense fibrous tissue which in the temporomandibular joint covers the articulating bones shows an arrangement of its fibers duplicating that of the fibrils in hyaline cartilage. The bundles of collagenous fibers show a radial course in the deep layer and a tangential course in the superficial layer *of the fibrous covering of both mandibular* condyle and articulating areas of temporal bone

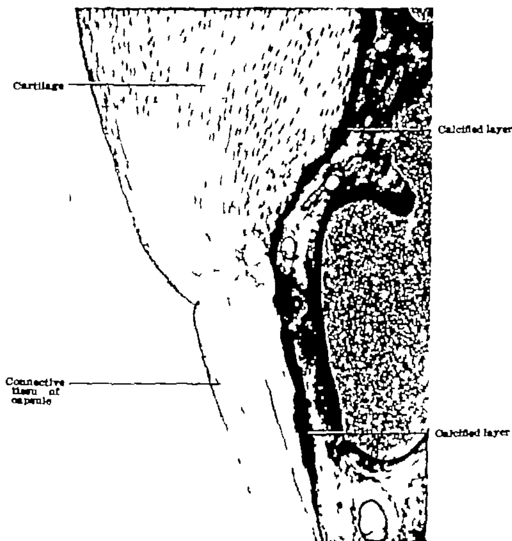


Fig 32.—Marginal zone of the articular cartilage and transition i t fibrous tissue of the capsule. Same specimen as shown in Fig. 30 Note the tangential arrangement of the cells and cell territories, the extension of fibrous tissue over a narrow area on the surface of the cartilage, and the continuation of the calcified layer covering the bone into the area of attachment of the fibrous capsule. (Original magnification X120 reduced to ⅝)

In the marginal zone of the articular cartilage the radial fibrils form a dense layer (Fig 32) This can be regarded as a zone of transition between the hyaline cartilage and the connective tissue of the articular capsule The arrangement *of fibrils and cells can be regarded as a functional adaptation* to the peculiar stresses of an articular cartilage which allows the gliding of one bone on the other under pressure.

The deepest layer of the articular cartilage is calcified The calcified zone is said to serve as the firm connection between cartilage and bone. It has been shown that this connection is considerably weakened by artificial decalcification The radial fibrils are anchored in the calcified zone with both their ends. They do not continue into the underlying bone.

The calcified layer does not end at the border of the articular cartilage It continues into the zone in which the synovial capsule is attached to the bone (Fig 32) The existence of a calcified zone in the deepest layer of the connective tissue of the capsule casts some doubt on the claim that the calcified cartilage has the function of securing the union between cartilage and bone Similar calcified layers are found in the deepest strata of the fibrous tissue covering the bony surface of the temporomandibular articulation. The explanation may be that calcification is a reaction of either cartilage or connective tissue adjacent to an aplastic surface of bone if it is under pressure The bone adjacent to the cartilage is a compact bone without Haversian systems. The osteocytes are round and have only few processes.

DEVELOPMENT OF BONES

In discussing the development of bone as a tissue the fact was stressed that there is only one type of bone formation. One should not refer to membranous and endochondral bone development unless it is clearly established that such division applies only to the development of bones as units of the skeleton. It would be more appropriate to classify the bones as (1) those which replace a temporary cartilaginous skeletal part (2) those which are not preceded by a cartilaginous organ and finally (3) those without a cartilaginous predecessor where, during their formation and growth cartilage is differentiated from connective tissue and then plays an important part in the growth of this type of bone Cartilage which forms skeletal parts prior to bone development is called primordial or primary cartilage cartilage which is differentiated during development and growth of bone should be referred to as secondary cartilage The division of development of bones—as distinct from bone development—into membranous and endochondral types is of great importance for the understanding of normal phenomena of growth as well as for an appreciation and proper classification of some diseases of the skeleton.

1. Bones which are preformed in cartilage and thus develop according to the endochondral type are those of the axial and appendicular skeleton (with the possible exception of the clavicle) and in the skull the ethmoidal bone and the inferior conchae and the bones at the cranial base with the exception of the medial lamina of the pterygoid process.

2. Bones which develop in connective tissue and are not preformed in cartilage are the parietal and frontal bones, all the bones of the upper face the squama of the temporal bone the tympanic bone, the medial plate of the pterygoid process of the sphenoid bone and the superior part of the occipital squama.

Some of these bones, for instance nasal bone maxilla and vomer develop in close proximity to the cartilaginous nasal capsule. They are however always separated from the cartilage by a layer of connective tissue

3 The mandible and possibly also the clavicle are membranous bones in which secondary cartilage develops at a later stage

Endochondral Development of Bones

The most typical example of endochondral development of bone formation is that of any one of the long bones of the extremities. The first sign of its development is a condensation of the mesenchyme to precartilage. Later the cells of this condensed area differentiate into chondrocytes, elaborating a hyaline intercellular substance and shaping a crude mold of the skeletal part



Fig. 31.—Development of an endochondral bone Metatarsal bone of a newborn rabbit. Note the swelling of the chondrocytes and the cartilage, the perichondral splint, and the beginning destruction of the cartilage and its replacement by invading connective tissue.

A General view (Magnification ×35.)

B. High magnification of the central part of the shaft. (Original magnification ×125 reduced to ¾)

The first sign of "ossification" is a degeneration of the cartilage at the middle of the shaft. The degeneration has to be characterized as an intracellular edema of the chondrocytes (Fig. 31). The cells enlarge considerably and seemingly in a short time by the intake of great amounts of fluid which appear as vacuoles in the cytoplasm and in the nucleus. The edema increases until the cytoplasm consists only of a faintly staining network and until the nucleus represents an almost empty vesicle, the chromatin being displaced to the periphery. During the same time the glycogen which had been stored in the chondrocytes disappears and phosphatase can be found in the cells.

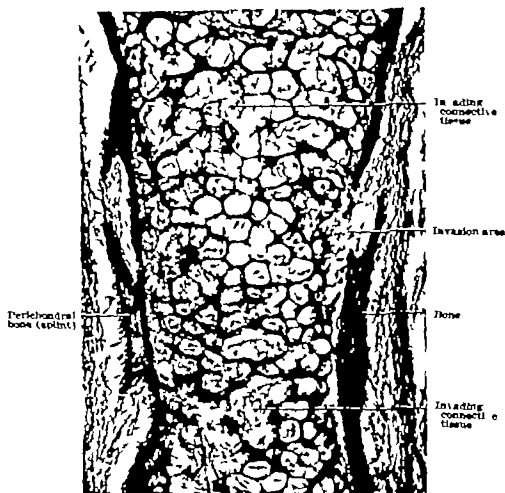


Fig. 31.—(For complete legend see opposite page.)

The swelling of the cells leads to a stretching of the intercellular substance which is thus transformed to a network of thin, widely spaced bars. The mechanical distention of the intercellular substance is one indispensable preparation for its removal. The second change by which the destruction of the cartilage is prepared is a change, in all probability a depolymerization, of the intercellular substance, accompanied or followed by its calcification. The change

in the intercellular substance of the cartilage is, most likely identical or at least similar to that occurring in osteoid tissue prior to its calcification. This view is strengthened by the finding that uncalcified cartilage and osteoid tissue show an identical metachromasia. The calcification occurs in the last phases of the swelling of the cartilage and is immediately followed by the invasion of connective tissue. The calcification seems to start in the thicker interterritorial bars and extends later into the thinner intraterritorial septa.

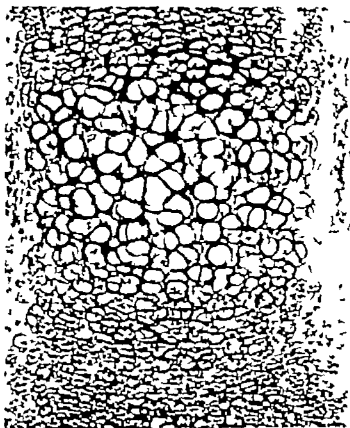


Fig. 34.—Central part of the shaft of a phalangeal bone of a newborn rabbit. Note the intracellular edema of the chondrocytes and the reduction of the intercellular substance to thin bars. (Original magnification ×330 reduced to ⅔.)

The first trabeculae of bone are formed in the connective tissue surrounding the middle portion of the shaft that is, in the perichondrium in direct contact with the cartilaginous model (Fig. 33). This perichondral "collar" of bone could be termed a perichondral *splint*. It encircles and supports the shaft where the cartilage has degenerated and calcified and is about to be resorbed. The formation of the perichondral splint and its extension always precedes the destruction of the cartilage model.

The destruction of the calcified area starts with the proliferation of the *periosteum covering the diaphyseal collar* (Fig. 33). The young richly vascularized tissue reaches the cartilage either between the trabeculae of the bony collar or by resorption of part of the perichondral bone. The resorption of the extremely thin bars of calcified cartilage and thus the opening of the capsules, is

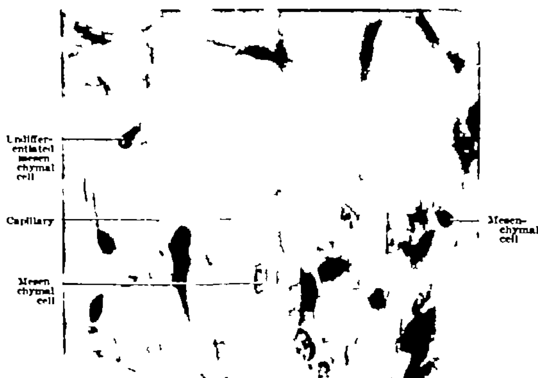
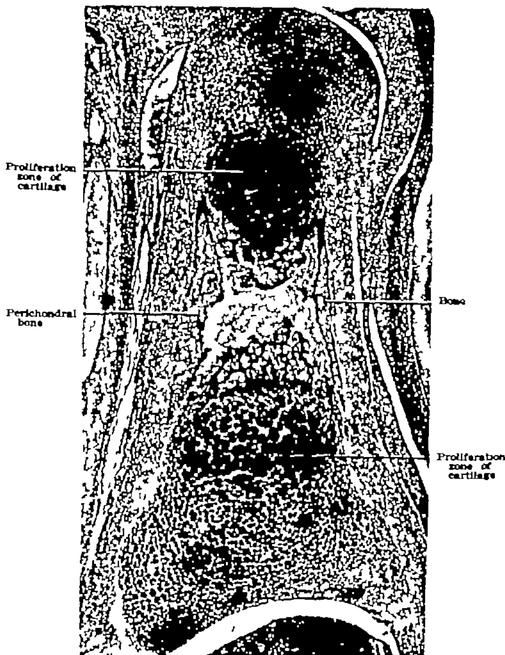


Fig. 35.—Beginning invasion of the cartilage capsules by connective tissue. Note the "undifferentiated" mesenchymal cell preceding and accompanying the proliferating capillary loops. (Original magnification ×750 reduced t)



Fig. 36.—Macrophages in opened capsules of the epiphyseal cartilage. Decalcified section of a tibia of a rat. (Original magnification ×750 reduced to ⅔.)



A.

Fig. 37.—Later stage in the development of an endochondral bone. Middle phalanx of a new born infant.

A General view showing the proliferating cartilage in both ends of the bone and the gradual degeneration and destruction of the cartilage closer to the primitive marrow cavity. The perichondral bone bridges the central defect in the cartilage. (Magnification ×45.)

B High magnification of the border zone between marrow and cartilage. Note the remnants of calcified cartilage at the surface of which bone is deposited. (Original magnification ×240 reduced to ⅘.)

the result of a proteolytic activity of cells of the proliferating connective tissue (Fig. 35) In all probability specialized mesenchymal cells are responsible for the destruction of the calcified cartilage in much the same way that osteoclasts destroy bone Though the observation of such cells covering the advancing capillaries is not always easy weighty arguments strengthen this interpretation. The most important argument is that the removal of the cartilage is prevented if the calcification fails. As in bone the depolymerization of the intercellular substance of cartilage is indispensable for the destruction of this

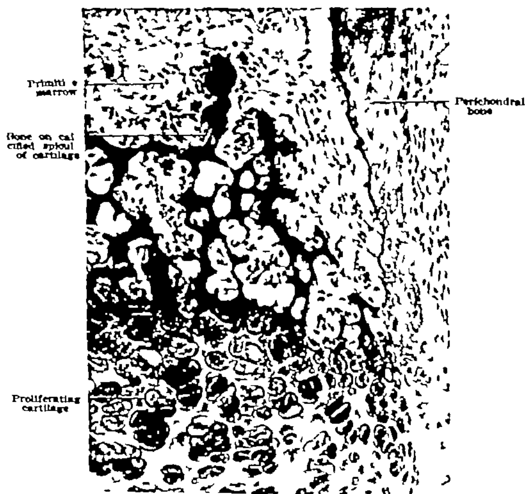


Fig. 37.—(For complete legend see opposite page)

substance by the activity of osteoclasts. Automatically calcification follows the depolymerization of the intercellular substance The change of the organic component is responsible for the change in the staining reaction of the calcified cartilage in decalcified sections to a strong basophilia.

Immediately before or at the time when the capsule of a cartilage cell is opened, the cell itself dies. The fragments of the cell are removed by macrophages which accompany and sometimes even precede the invading capillaries (Fig 36)



Fig. [illegible].—Advanced stage in the development of an endochondral bone. Proximal phalanx of a newborn infant. (Magnification ×[illegible].)

When the described invasion of the degenerated cartilage has proceeded to some degree remaining heavier bars of calcified cartilage are removed by true giant cells which are identical with osteoclasts and are sometimes termed chondroclasts.

Shortly after the central part of the cartilaginous shaft is resorbed and an irregular primary marrow cavity has been formed, bone formation commences in the connective tissue which fills the marrow cavity Bone is deposited on the surface of the remaining calcified cartilage (Fig 37) Formation of this bone goes through the different stages that were previously described formation of primary and secondary osteoid tissue and its final changes and calcification. The primitive marrow cavity is then bound by slender delicate irregular bony trabeculae many of which contain a core of calcified cartilage (Fig 37) primary spongiosa

In the course of formation of bone in the young connective tissue invading the cartilage the opened cartilage capsules are frequently filled with bone tissue One or more osteocytes can then be seen in the area formerly occupied by an edematous chondrocyte This picture of a more massive tissue consisting of a mosaic of calcified cartilaginous intercellular substance and bone can be seen in the growth area of all cartilage bones. It is especially noticeable in the metaphyseal areas of long bone but sometimes it is even found in the primary compacta of the near metaphyseal part of the shaft. Since however resorption of the primary spongiosa occurs at a rapid rate, in part correlated to the development and enlargement of the central marrow cavity this specific variety of bone deposition is not a striking feature of the development of long bones.

In bones, however where the columnar arrangement of cartilage cells is not highly developed where therefore the invasion of the cartilage occurs in a more irregular way the picture of cartilage capsules entirely filled with bone is much more obvious. If in addition, the reconstructive resorption of the primary spongiosa is delayed, the cartilage bone mosaic dominates the area of newly formed bone. Examples of this can be seen in the condyle of growing mandibles in the bones of the base of the skull and in vertebrae (Figs. 39 and 68)

There is one bone in which the discrepancy between formation and resorption is highly exaggerated It is the otic capsule where resorption of the primary bone is negligible Here part of the capsule consists of compact bone including variably large islands of calcified cartilaginous intercellular substance, the capsules of which are completely filled with bone (see page 87) Such a mosaic tissue was held to be characteristic for the bone of the otic capsule and the auditory ossicles. It is believed to be a specific bone and it was termed intrachondral bone The assumption that this type of tissue is characteristic of the otic region is however erroneous. It is also confusing to differentiate intrachondral and endochondral bone As a matter of fact, the enclosure of calcified cartilaginous intercellular substance into the newly forming bone is a general feature of the primary spongiosa Th-

The first sign of epiphyseal ossification is the degeneration calcification and resorption of the cartilage in the center of the future epiphysis around the blind end of the vascular canal Connective tissue around the blood vessels of the cartilage proliferates, new vessels are formed, and the central part of the cartilage is gradually replaced by spongy bone. Dates of ossification are characteristic for each bone and important for the determination of the skeletal age of an individual.

The further progress in the development of a long bone is seen in the replacement of the cartilaginous extremities of the bones by spongy bone, development of compact bone in the primarily spongy cortical layer of the shaft



Fig. 41.—Entrance of blood vessels in a strand of connective tissue into the cartilaginous pelvic bone of a two-year-old child. (Original magnification ×65, reduced to ½.)

and development of a uniform marrow space in the central part of the shaft, the ends of which remain cancellous. The extremities are now termed epiphyses, the shaft is the diaphysis, and the ends of the diaphysis are known as metaphyses. The still-growing cartilage which is spared degeneration and replacement by bone is found in two typical locations (1) the extremities remain covered by articular cartilage (2) discs of cartilage persist, separating both ends of the diaphysis, that is, the metaphyses from the epiphyses. The discs are called epiphyseal cartilages.

Growth of Tubular Bones

Transverse Growth.—The shaft of a long bone grows in thickness by *simple apposition of new layers of bone* upon the *periosteal surfaces* of the shaft (Fig 42) Concomitantly two processes can be observed (1) resorp-

tion of the compact cortical layer from the marrow space which maintains a certain ratio of the diameter of the shaft to the thickness of the compact bone (2) gradual replacement of the circumferential lamellae which are formed by periosteal apposition by Haversian systems from within (Fig 43) In the connective tissue of an Haversian canal adjacent to the circumferential lamellae osteoclasts differentiate resorbing parts of the Haversian system and parts of the circumferential lamellae. After some time resorption subsides and new apposition of bone takes place building new Haversian systems (Fig 44) By repetition of this sequence of resorption and reformation, secondary tertiary etc. Haversian systems develop The continual reconstruction of the compact



Fig. 42.—Transverse growth of a long bone. Ground cross section through the humerus of a rhesus monkey which had received four injections of alizarin S red. The bone formed at the time of each injection is stained red. The successive lines are parallel to each other and to the surface of the bone. (Original magnification X115 reduced to ¾) (Specimen courtesy Dr M. Massler)

bone can be recognized by the presence of reversal and resting lines and by the fact that some interstitial lamellae betray their origin from circumferential lamellae by the inclusion of Sharpey s fibers.

The descriptions of the transverse growth of a diaphysis by continuous apposition at the outer periosteal surface and resorption at the inner or medullary surface is highly diagrammatic. In reality two facts obscure this simplified picture. It has to be recognized that, quite generally resorption proceeds in waves, each of which is carried farther than the necessity of eliminating a certain part of bone seems to warrant This causes the alternation of resorption and repair during the so-called "modeling resorption." It should be

mentioned that also resorption caused by pressure does not only remove an amount of bone sufficient to bring the pressure back to normal but always destroys more bone in order teleologically speaking to create conditions and space for the necessary reconstructive repair

The fact that the hollowing out of the marrow space occurs in waves, each overshooting its mark must result in alternating periods of resorption and reconstructive apposition on the inner or medullary surface of a diaphysis. The complications are enhanced by the fact that periods of resorption and apposition do not always occur for the entire extent of the diaphysis at the same time

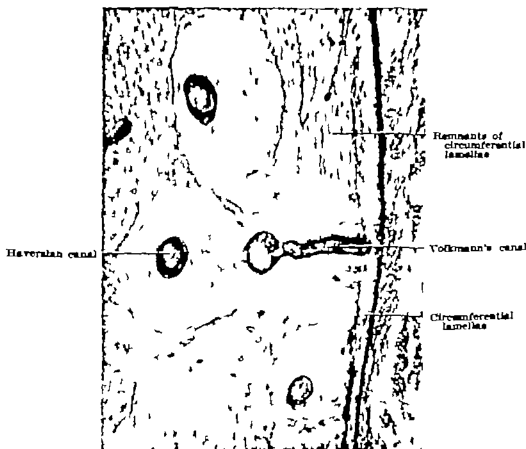


Fig 42.—Internal reconstruction of compact bone. Lower jaw of a young adult, sixteen years of age. Decalcified section. Hematoxylin-eosin stain. Advanced stage of replacement of circumferential lamellae by Haversian systems. (Original magnification X180; reduced to ⅘.)

In the special case of transverse growth of a long bone, the state of the inner or medullary surface is further complicated by the influence of changes in the shape of the entire bone upon the progress of resorption or apposition on any one of its surfaces. If a bone is curved, its growth is possible only by maintaining a relation between length of the shaft and radius of its curvature In other words, the curvature has to decrease with the growing radius, and

this change necessitates a characteristic distribution of areas of apposition and resorption. In other cases the relative curvature of a bone may increase or decrease during the period of growth and this change also is achieved by an exact correlation of apposition and resorption on outer and inner surfaces. In some bones quantitative differences of apposition in different areas may suffice to effect the necessary changes in the shape of the bone

The interpretation of any section through a long bone can be correct only if one takes into account the complications which arise (1) from the over extension of resorption and the consecutive reparative or reconstructive apposition and (2) from the morphologic growth changes of the individual bone.

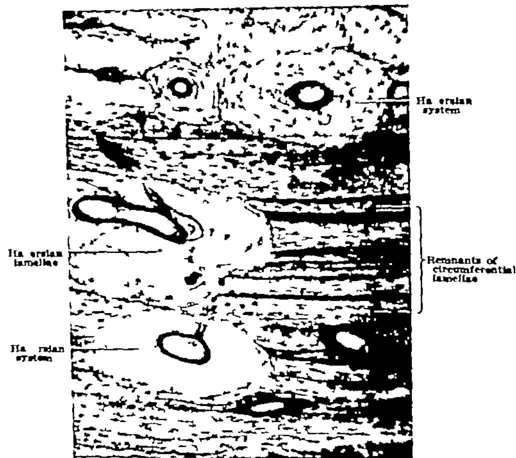


Fig. 44.—I ternal reconstruction of compact bone. Lower jaw of an adult. Decalcified section. Hematoxylin-eosin stain. The circumferential lamellae are partly resorbed and replaced by Ha rsian systems. (Original magnification ×130 reduced to %.)

Longitudinal Growth.—Diagrammatically a growing long bone consists of a bony shaft and two bony extremities, the epiphyses, which serve for the articulation with the adjoining bones. The shaft can be divided into a tubular middle part the diaphysis, and two spongy parts at either end, the metaphyses. The metaphysis is separated from the epiphyses by a plate of hyaline cartilage the *epiphyseal plates*. The epiphysis is covered on its free

surface by the articular cartilage The longitudinal growth of such a bone is primarily achieved by interstitial growth of the epiphyseal and articular cartilages, in other words, by the growth of the derivatives of the cartilaginous model *A thickening of these four plates of cartilage brings about a true lengthening of the bone as an organ.* The partial replacement of the growing cartilaginous plates by bone does not lead to a lengthening of the bone as a whole but to lengthening of the bony shaft and bony epiphyses and to the functional solidification of the bone

TABLE II

LONGITUDINAL GROWTH OF A LONG BONE

LOCALIZATION OF GROWTH	EFFECT	MECHANISM OF GROWTH
Growth of epiphyseal and articular *cartilages*	Lengthening of the bone as a whole	Interstitial growth of cartilage
Replacement of a layer of epiphyseal cartilage adjacent to metaphysis by bone.	Lengthening of the bony diaphysis	(a) Degeneration of a zone of cartilage (b) Calcification of degenerated cartilage (c) Resorption of calcified cartilage (d) Appositional growth of adjacent bone
Replacement of a deep layer of articular cartilage by bone	Lengthening of the bony epiphysis	

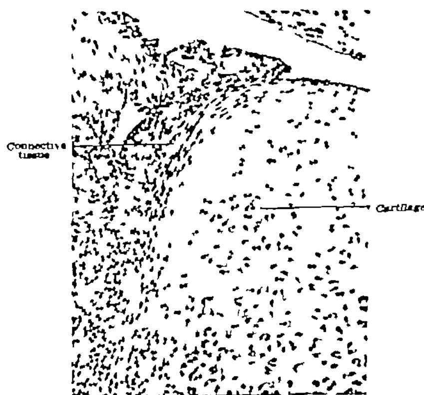


Fig. 43A.—Appositional growth of the cartilaginous head of a phalanx of a newborn infant. Not the transition between connect e tissue ad cartilage. (Original magnification ×240 reduced to ⅘.)

In Table II are summarized the factors which are necessary in the complicated process of longitudinal growth of a long bone. It is of greatest importance to visualize the different factors active in longitudinal growth and their specific contribution to the growth of a bone. Only then is it possible to understand the influence upon skeletal growth of specific disturbances of any one of these factors.

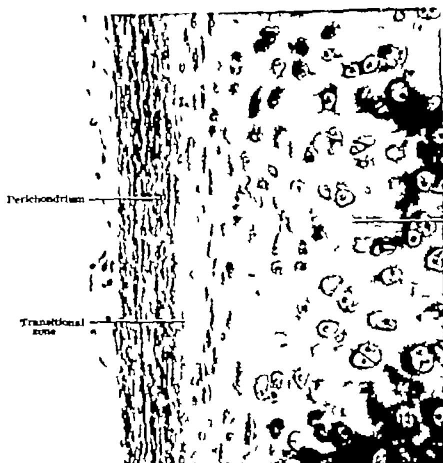


Fig. 45B.—Appositional growth of cartilage. Longitudinal section through the costal cartilage of a young guinea pig. Note the transition between connective tissue and cartilage in the deepest layer of the perichondrium. (Original magnification X350, reduced to ⅔.)

Longitudinal Growth of the Diaphysis.—The longitudinal growth of the shaft entails the following processes:

1. Interstitial growth of the epiphyseal cartilage in the direction of the longitudinal axis of the bone, thus lengthening it as a whole.

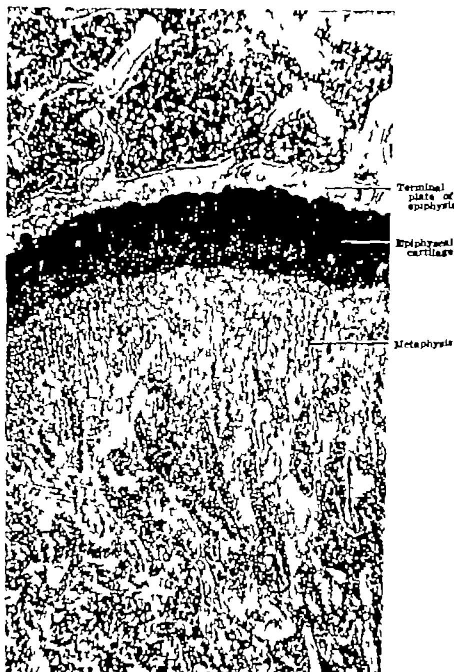
2. Degeneration and calcification of the layer of the epiphyseal cartilage adjacent to the metaphysis.

3. Resorption of the calcified layer of epiphyseal cartilage.

4. Apposition of spongy bone replacing resorbed cartilage.

Cartilage grows interstitially as well as appositionally. Interstitial growth occurs by mitotic division of cartilage cells and production of additional hya

line intercellular substance by these cells. The two daughter cells are at first found in one capsule. Later they produce a thin plate of hyaline substance dividing the capsule in two. Repeated cell division leads to the formation of



A.

Fig. 46.—Epiphyseal cartilage of a young rat.

A. Note the terminal plate of a bone in the epiphysis the columnar arrangement of the cells in the epiphyseal cartilage and their gradual enlargement toward the metaphysis the dense longitudinal bone trabeculae in the metaphysis, primary spongiosa, and the loose arrangement toward the diaphysis, secondary spongiosa. (Magnification ×46.)

B. High magnification of the epiphyseal plate. (Magnification ×200.)

clusters of cells separated from each other by narrower plates, and from neighboring clusters by wider plates, of intercellular substance. The cells in one cluster are the offspring of one cell.

Appositional growth of cartilage takes place on those surfaces of cartilage which are covered by perichondrium (Fig. 45). There is a gradual



B.

Fig. 46.—(For complete legend see opposite page.)

transition from fibroblasts in the deeper layers of the perichondrium to chondrocytes in the superficial layers of the cartilage.

There is a most important principal difference between appositional and interstitial growth The former depends primarily on the *mitotic division of* differentiated cells, the latter on the differentiation of undifferentiated cells. An example of the significance of this difference is the inhibition of interstitial growth of cartilage in genetically caused chondrodystrophy while in this disease appositional growth of cartilage proceeds undisturbed.

It is of greatest importance *to realize that cartilage can grow in some* dimensions only by interstitial growth, whereas its growth in other dimensions may be interstitial as well as appositional A costal cartilage can grow in length only by interstitial growth, but interstitial and mainly appositional growth contribute to its gradual thickening Epiphyseal and articular cartilage can expand in the longitudinal axis of the bone only by interstitial growth. The articular cartilage widens, however by appositional growth at its borders, where a more or less narrow zone is covered by an extension of the articular capsule which functions as perichondrium. The epiphyseal plate shows both appositional and interstitial growth. The part of the plate which is not surrounded by the splint shows addition of new chondrocytes from the perichondrium. The area where the splint ends and the appositional growth of the plate occurs can be seen in longitudinal section as a notch known as the Ranvier s encoche '

Once included within the epiphyseal plate the chondrocytes undergo repeated mitoses to form cell columns. The plane of division of the chondrocytes, *and therefore the arrangement of the cell columns, reveals the con*tribution of the epiphyseal plate to the growth of a bone. Columns are either arranged in the long axis of the bone or diverge toward the metaphyses, showing thus that the interstitial growth of these chondrocytes seems to increase the length as well as the width of a bone. The arrangement of these cell columns varies at different periods of growth. In the younger stages the divergence of columns is specially marked.

The epiphyseal plate can be divided into several zones (Fig 46) Adjacent to the epiphysis is the thin germinal layer in which small cartilage cells are irregularly distributed. By mitotic division some of the cells start to form territories which are clearly visible in the next zone, which can be designated as proliferating zone. The cells of this zone divide in such a way that they arrange themselves in longitudinal rows of from eight to sixteen flat wedge-shaped cells. The plane of division of these cells is parallel to the longitudinal axis of the bone. By a peculiar mode of growth the daughter cells soon form a pair of wedge-shaped discs. Continued division and overlapping growth lead to the formation of the longitudinal columns of chondrocytes (Fig 46) The cells of one column are closely packed and are separated from one another by thin bars of intracolumnar hyaline ground substance, while one territory is separated from the other by a greater amount of intercolumnar intercellular material. The next zone is that of growth of the cells and intercellular substance

(Fig 47) Then follows the zone of intracellular edema which continues without sharp boundary into the zone of calcification (Fig 48) The edema of the chondrocytes leads to an enormous increase in size of each cell territory and a stretching and thinning of the intercellular substance Finally, high columns of large cells, separated by thin crossbars result The interterri torial or intercolumnar bars of hyaline substance are likewise stretched and

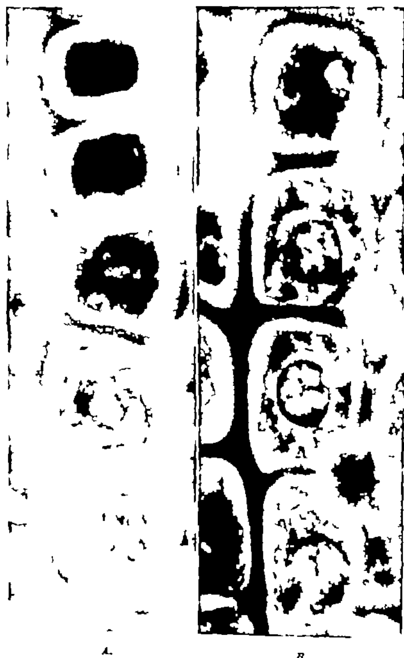


Fig 47 —Columns of cartilage cells from the proximal epiphyseal plate of a tibia of a rat. (Magnification × 50)
A Growing and degenerating chondrocytes.
B Beginning degeneration.

thinned but remain generally thicker than the intraterritorial crossbars. That the edema enlarges the cells mainly in the longitudinal direction of the bone is caused by their disclike shape at the end of their growth period. The edema causes the cells to assume roughly a spheroid shape.

In the zone of calcification the calcium salts are first visible in the intercolumnar bars and later in the intracolumnar bars. The delayed calcification of the crossbars may have given rise to the assertion that they remain uncal-



Fig. 48 —Columns of cartilage cells from the proximal epiphyseal plate of a tibia of a rat. Progressive intracellular and intranuclear edema and degeneration of the cartilage cells. (Magnification ×750.)

cified. Next to the metaphysis the destruction of the cartilage can be observed whereby at first the intracolumnar septa are removed and the capsules of one column opened and then invaded by proliferating connective tissue and capillary loops.

The resorption or dissolution of the thin crossbars of cartilage seems to occur by the activity of uninuclear cells which are often found surrounding the capillaries. These cells, in all probability derived from the undifferentiated

nchymal cells, are characterized by their eosinophilic cytoplasm and can be homologized with osteoclasts. The removal of the stronger interterri l septa is due to the action of uninucleated and multinucleated chondro- s. Spicules of calcified cartilage persist always, forming the core of the de- ping bone trabeculae (Fig 49) The cancellous bone of the metaphysis that ains remnants of *cartilage is termed primary spongiosa.* In the first years le bone of a coarse-fibrillar type is laid down upon the cartilaginous spicules.

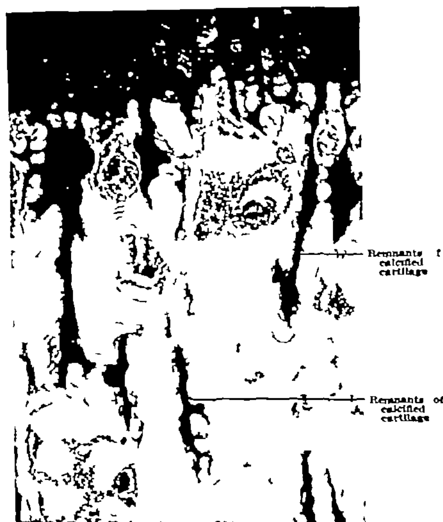


Fig 49.—Metaphysis of the humerus of an eleven-yea -old child. Not the remnants of fied cartilage in the center of the bony trabecula. (Original magnification X150 reduced ½.)

later years mature lamellated bone gradually replaces the immature bone and newly deposited bone is also mature and lamellated. When bone formation s progressed for some time an internal reconstruction takes place in this re- n. The compact cortical layer of the diaphysis lengthens toward the epiphyseal rtilage The marrow spaces in the external layers of the metaphysis are led with bone and new layers of circumferential lamellae are added at the

same level. At the same time the primary spongy bone is gradually resorbed and with it the last remnants of calcified cartilage in the core of the longitudinally directed trabeculae In part, the extending marrow space of the shaft occupies the site of the resorbed trabeculae and in part, new trabeculae of mature bone are laid down in a functional arrangement, secondary spongiosa.

Morphogenesis of Bones.—The elaboration of the definite shape of any *bone is the effect of three processes. The first one is a differential growth of* the cartilaginous model. It can be shown, for instance that the proximal end of the tibia grows eccentrically the proliferation is directed almost entirely posteriorly This differential growth of the cartilage accounts for the rough outlining of the proximal curvature of this bone This growth phenomenon which is mainly localized to the ends of long bones, may also be responsible for the inclusion of blood vessels in the cartilaginous epiphyses prior to the beginning of epiphyseal ossification.

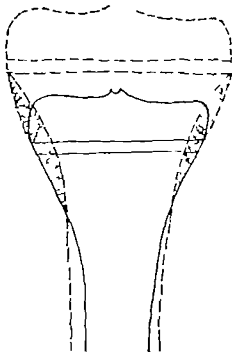


Fig. 50—Diagram f th growing end of a long bone (tibia) to show the amount f modeling resorption (stippled areas) necessary to maintain the normal shape of the growing shaft.

The second process, modeling the surfaces of a bone, is that of differential growth of the bone tissue that is, patterned apposition of bone In this way crests, ridges, tubercula and tuberosities develop

There is, finally the process which has been aptly called modeling resorption. An example can be observed at the epiphyseal ends of tubular bones. The shaft of most long bones flares toward the epiphyseal disc (Fig 50) which is therefore wider than the shaft in its middle part. Growth of the cartilage and its replacement of bone create a plump clublike swelling of

the shaft The narrow cylindrical shaft can be formed only by a modeling resorption of the flaring metaphyses from the periosteal surface It has to be remembered that resorption of bone is an integral part of skeletal growth.

Longitudinal Growth of the Epiphysis.—The expansion of the epiphysis by endochondral growth (that is, by replacement of the growing articular cartilage by bone) contributes *to a lengthening of the epiphysis*. The changes in the epiphysis in principle resemble those in the diaphysis. The articular cartilage grows in thickness by interstitial growth and widens its surface area by appositional growth at its border The cartilage cells appear in columns



Fig. 51 —Growth of the epiphysis of a long bone Articular cartilage of a tibia of a rat. Note the proliferation, swelling, and degeneration of the cartilage cells, the destruction of the cartilage by cells of the invading connective tissue and its replacement by bone. (Original magnification ×250 reduced to ⅘)

at right angles to the articular surface (Fig 51) Before new bone trabeculae are formed, the innermost layer of the articular cartilage degenerates, calcifies, and is partially resorbed. In the epiphysis, the immature bone, with its trabeculae enclosing remnants of cartilage is soon resorbed and replaced by mature lamellated bone.

Terminal Plate.—The epiphyseal cartilage does not contribute to the growth of the epiphysis. The epiphyseal surface of the epiphyseal cartilage is therefore inactive The bone of the epiphysis shows a characteristic arrangement where it borders the epiphyseal cartilage (Fig 46) The bony trabeculae of the

epiphysis unite in this zone to form a thin continuous plate sealing, as it were, the epiphyseal marrow spaces against the epiphyseal plate. This bony plate adjacent to the cartilage is called the terminal plate.

EPIPHYSEAL UNION —The interstitial growth of the epiphyseal cartilage is at first rapid enough to maintain the thickness of the disc of cartilage, despite the continual destruction and replacement by bone in the metaphyseal zone. Later however the rate of cartilage growth is reduced so that gradually the cartilaginous disc is narrowed until finally the entire epiphyseal cartilage is replaced by bone and a bony union is established between diaphysis and epiphysis.

The site of bony union between the diaphysis and epiphysis remains visible for a long time as a sclerotic ' zone. This layer of compact bone at the site of synostosis between shaft and extremity is mainly the persisting terminal plate of the epiphysis. The disappearance of the terminal plate and its final functional reconstruction and thus the establishment of a functional unity of the bone need several years.

It should be clear that the fate of the two cartilaginous plates, namely epiphyseal and articular cartilage differ in man at the end of general growth. At this time both cartilages cease their proliferation. While the replacement of the cartilage by bone continues on the metaphyseal surface of the epiphyseal plate replacement of the articular cartilage by bone ceases soon after the articular cartilage has stopped growing This difference explains, of course the disappearance of the epiphyseal and the persistence of the articular cartilage

CONTRIBUTION OF THE EPIPHYSEAL PLATES TO THE LONGITUDINAL GROWTH OF INDIVIDUAL BONES.—The diagrammatic idea is still widespread, that the two epiphyseal plates between the shaft and extremities of a long bone contribute an equal share to its growth, in spite of exact observations which clearly demonstrate the fallacy of this concept. This leads in some instances to almost grotesque assumptions. The obliquity of the neck of the femur makes it obvious that the proximal epiphyseal plate cannot contribute very much to over-all elongation of the femur and serves primarily to lengthen the neck. Some authors still believe that the distal epiphyseal plate cannot contribute more than one-half to the lengthening of the femur shaft. They therefore have to assume extensive apposition and resorption on the superior and inferior surfaces of the head and neck, respectively (Fig 52) The unwillingness of some authors to ascribe the longitudinal growth of a bony shaft to one epiphysis only is hard to explain since it is well known that metacarpal and metatarsal bones and phalanges possess only one epiphyseal plate

A study of the diagrams on the growth of the femur which are still to be found in modern textbooks on anatomy and histology proves at first glance that the idea of apposition and resorption along the entire length of head and neck is untenable Such resorption would have to remove also the articular cartilage at the inferomedial circumference of the head. Resorption of cartilage from its free surface is, of course, utterly impossible. The propounders

of the apposition resorption theory have moreover, forgotten that roentgenograms which show growth lines (Fig 53) prove unequivocally that the femur grows at its lower epiphyseal plate at least twice as fast as the tibia at its upper end. The first diagram of Keith by which he intends to show the impossibility of a shift of the femur head during growth is therefore the true though diagrammatic picture (Fig 52, A) The longitudinal growth of the shaft of the femur occurs almost entirely at its distal epiphyseal plate

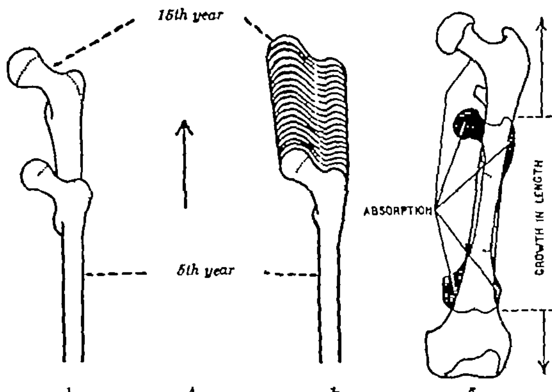


Fig. 52.—Diagrams of the growth of the femur

A 1 Upper end of femur of five-year-old child, above which is indicated the position which the head and the neck of the bone will occupy at fifteen years. 2. The form which it would have assumed had there been no remodeling. The arrow indicates the direction of appositional growth. (After Keith.)

B bone is deposited on the upper aspect of the neck of the femur and absorbed on the lower It is obvious that growth at the upper metaphysis of the femur will lengthen the neck only (After J C. Boileau Grant.)

Such inequalities of epiphyseal growth at the two ends of a long bone are also especially pronounced in the two bones of the forearm. Since the proximal epiphysis of the ulna consists of the tip of the olecranon only the ulna could almost be described as having only a distal epiphysis in so far as the growth of the shaft is concerned Consequently the ulna grows in length almost entirely by the growth of the distal epiphyseal plate. Probably to avoid a shifting of the growing shafts of radius and ulna against each other the longitudinal growth of the radius adapts itself to that of the ulna, so that here too the distal epiphysis contributes at least three times as much to the longitudinal growth as does the proximal epiphysis In some long bones however

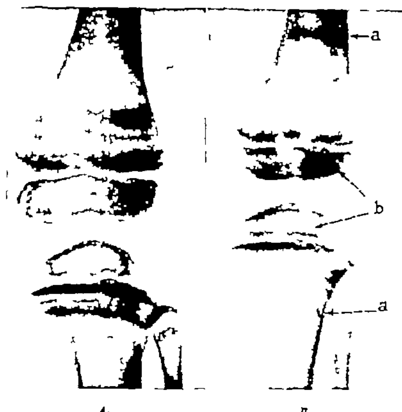


Fig. 53.—Roentgenograms of the knee. Multiple lines of arrested growth as a result of intermittent administration of phosphorised cod liver oil. *B* was taken four years later than *A*. Note that the difference in the distance between the lines in the femur is about twice that in the tibia. (After Siegling.)

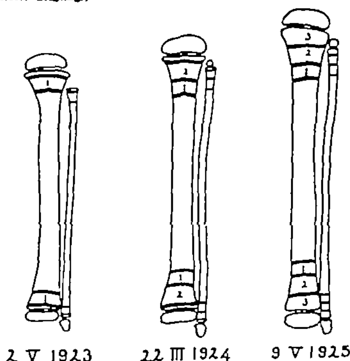


Fig. 54.—Three stages in the growth of the leg bones of a young girl, showing lines of arrested growth due to three successive attacks of severe illness. The increments at proximal and distal ends of tibia and fibula are equal. (After H. A. Harris from J. C. Boileau Grant.)

growth is more nearly equal at the two ends The proximal and distal epiphyses of the tibia and fibula, for example, grow at approximately the same rate of speed (Fig. 54) The proximal epiphysis of the humerus however grows much faster than the distal one.

An excellent means of visualizing the difference in growth rate of epiphyses is a study of roentgenograms of the bones of children who show epiphyseal growth lines caused by medication with phosphorus or intoxication by lead and other metals. The distance between growth lines at various ages reveals the relative rate of growth in different bones.

It is interesting that the ossification starts in that epiphysis of a long bone which contributes most to its longitudinal growth. The epiphyseal cartilage at this point disappears last. In the lower extremity the epiphyses at the knee joint appear first the center of ossification in the distal epiphysis of the femur is, in fact the only epiphyseal bone present in a normal newborn infant. In the arm the epiphyseal ossification commences earlier in the head of the humerus and the distal epiphyses of the ulna and the radius.

Histogenesis and Histology of the Otic Capsule

The otic capsule consists of a thin layer of compact, almost ivory like bone enclosing the otic labyrinth and is, for its greater part, deeply embedded in the petrous pyramid of the temporal bone It conforms roughly to the complicated shape of the membranous labyrinth, enclosing in the vestibule the utriculus and sacculus, forming the bony cochlea to house the cochlear duct and three semicircular bony tubes for the three semicircular canals. Its outer surface is almost everywhere fused to the bone of the pyramid, while the inner surface is lined by a thin periosteum (not endosteum) which bounds the periotic spaces.

The otic capsule is preformed in cartilage which is gradually replaced by bone Although this process of ossification of the otic capsule follows in principle the sequence of events described earlier there are several peculiarities characteristic for this bony part They deserve a discussion also because they may point the way to a better understanding of certain pathologic changes of the skeleton

The cartilaginous otic capsule is fully formed at a time when the membranous labyrinth, especially the semicircular canals are still growing at a very fast rate Growth of the labyrinth entirely enclosed in a capsule of hyaline cartilage is, of course possible only by a simultaneous expansion and growth of the capsule This entails correlated appositional and destructive changes of the capsule If, for instance a growing semicircular canal increases its radius, it is clear that the cartilage at its convex peripheral surface has to be destroyed, while new cartilage forms at its concave central surface

The destruction of hyaline cartilage during this period of development is entirely different from the mode of removal of cartilage that precedes its replacement by bone In the latter process there is a hydropic degeneration or

edema (not hypertrophy) of the chondrocytes and a calcification of the intercellular substance. Only then is the intercellular substance removed by the activity of the osteoclast like cells while the chondrocytes whose capsules are opened necrotize their remnants are then removed by macrophages.

During the growth of the cartilaginous otic capsule the destruction of cartilage is by direct mucoid degeneration, and then by necrosis of the hyaline cartilage without preceding enlargement of chondrocytes or calcification of the intercellular substance. The necrotic debris of cartilage is removed by macrophages.

It is highly probable that the disappearance or 'atrophy of large parts of Meckel's cartilage and the cartilaginous nasal capsule occurs also by necrosis and phagocytic removal of the cartilage



Fig. 55—Section through the otic capsule of a newborn infant, showing the endosteal A endochondral, B and periosteal, C layers of bone. (Courtesy Dr Francis L. Lederer)

This mode of destruction of cartilage may also have a bearing on observations in the epiphyseal cartilage of rachitic animals. In these animals, calcification of cartilage does not occur and therefore the cartilage is not as a rule resorbed. However under certain circumstances, resumption of cartilage resorption has been observed. It is highly probable that these observations can be explained by necrosis of cartilage and not by its resorption

The replacement of the fully grown cartilaginous otic capsule by bone occurs in principle in the same way as in other cartilage bones. It should first be mentioned that, as for instance in long bones, perichondral bone forms

tion also plays its role in the development of the bony otic capsule forming an outer and an inner periosteal layer It is, therefore only the middle layer of the otic capsule which develops by replacement of cartilage (Figs. 55 and 56) In this process, enlargement of the chondrocytes by intranuclear and intracellular edema and calcification of the intercellular substance precede the resorption of the cartilage and the invasion of the excavated spaces by proliferating connective tissue Since there is no formation of cell columns, the paths of invasion are more tortuous than in the epiphyses of long bone. It is this tortuosity which causes the more prominent appearance of what has been unnecessarily termed

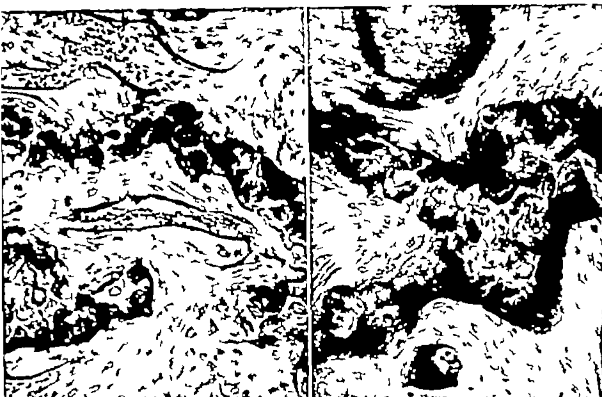


Fig. 56.—Otic capsule of a newborn infant. Higher magnification of two areas of Fig. 55. Remnants of calcified cartilage whose capsules are filled with bone ("intrachondral bone") (Dr Francis L. Lederer)

intrachondral bone, that is, bone tissue entirely filling empty lacunae of the cartilage A second reason why this filling of lacunae by bone is here so conspicuous is the severe retardation of resorptive and reconstructive processes in the otic capsule

The retardation of resorption of the primary trabeculae and, therefore their persistence into adult life causes also the persistence of the many formed remnants of calcified intercellular substance of cartilage enclosed in bone and enclosing bone

Though resorption lines can be seen on many surfaces of the primary trabeculae the destruction is outweighed by the apposition of new bone thickening the trabeculae and narrowing the primary marrow spaces, until a

very dense compact bone results which is of almost ivory like consistency While much of this bone is immature bone the bone gradually filling the marrow spaces, is, though not lamellated bone more highly differentiated than immature bone. Once the otic capsule has fully developed, any signs of internal *reconstruction by balanced resorption and apposition seem to be almost* negligible It is this lack of removal and replacement of bone so prominent in the entire skeleton, which characterizes the otic capsule more than anything else

Membranous Development of Bones

Formation of bone tissue in a membrane bone proceeds in the same way as in bones replacing cartilage, yet the development and growth of a membrane bone as a skeletal unit is by far simpler than that of endochondral bone. This is explained by the fact that this skeletal part is not preformed in cartilage but develops in a condensation of the embryonic mesenchyme. The bones of the cranial vault exemplify this type of bone development.

The parietal bone, for example, develops in the membranous capsule of the brain from a center of ossification. Here corresponding to the most prominent central area of the completed bone, the first slender bone trabeculae develop in the connective tissue. They consist of immature coarse fibrillar bone. These trabeculae radiate from the center of ossification and soon form a circular *platelet of bone with a thin irregular border Thus bone grows by* apposition on its outer and inner surfaces and at its borders For a considerable period it is composed entirely of spongy bone, but gradually an outer and an inner layer of compact bone develop The primary coarse fibrillar bone is replaced by mature lamellated bone, although for a long time the bone added at the sutural borders is of the immature coarse fibrillar type. The surface of the bone is rough at first and clearly shows the radial course of the trabeculae. Later it is smoothed by the apposition of a compact layer

When two adjacent bones of the skull come into close relation, a suture develops between them It is relatively wide at first and the union may be described as a syndesmosis between the two bones. The sutural connective tissue is a remnant of the membranous capsule of the brain and connects the outer and inner periosteum of the two bones. This layer of connective tissue is gradually reduced in thickness and the simple straight sutural line may also undergo extensive complications by the formation of interdigitating processes of the two bones (serrated suture)

Growth of Membranous Bones

A membranous bone of the skull may grow on the free surfaces or at the sutures. Which of the free surfaces is the site of apposition or resorption, and to what extent this varies in the different bones of the skull, depends mostly upon the age of the individual.

Sutural Growth.—Sutural growth is generally seen as appositional growth on the opposing sutural surfaces by which a spreading ' of the suture is ac

complished. Some authors, however put the emphasis on surface growth only and do not consider bone apposition at the suture as a primary spreading increment but as a secondary filling in of the space that is opened by surface apposition and resorption

In reality the sutural growth is initiated by a proliferation of the sutural connective tissue just as cartilaginous growth precedes the growth of the bony diaphysis or epiphysis.

The role of the proliferating sutural connective tissue in cranial growth is, therefore identical to that of the proliferating cartilage in basal synchondroses.

Longitudinal growth of a long bone is effected by the growth of its cartilaginous model Epiphyseal and articular cartilages are of course parts of this growing model that have not been destroyed and replaced by bone If one visualizes the primary role of the preosseous tissue in the growth of bones, the basic principle of cranial growth becomes immediately clear Here in the cranium, that is, skull without mandible and auditory ossicles, the preosseous tissue is partly cartilage as at the base partly membranous as, for instance at the cranial vault After ossification has progressed, the basal synchondroses are the remnants of the cartilaginous, the sutures, or better the sutural syndesmosis, the remnants of the membranous parts of the cranial model and it is their proliferation that is responsible for the over all growth of the cranium for instance, for the enlargement of the brain capsule Epiphyseal, articular basicranial cartilages and sutural connective tissue are therefore identical in their biologic significance as sites of growth. It also becomes apparent that the single bones of the cranium cannot be likened to other bones of the skeleton but rather to the bony parts of a developing and growing bone Biologically speaking the cranium is one bone

There is no doubt that sutural growth is a primary "spreading" of the suture since apposition of bone can be observed over the entire area of a sutural surface. If sutural growth were but a filling in, secondary to apposition of bone on convex surfaces, only the part of a suture close to the external surface of the bones could show bone apposition.

The histologic structure of the sutural tissue reveals its adaptation to its double function of uniting firmly the two neighboring bones and providing the site of proliferation for the "spreading" of the suture (Fig 57) It consists of three layers. The peripheral layers adjacent to the bones consist of dense connective tissue, the fibers of which are parallel to each other and at right angles to the sutural surfaces of the bones. They continue into the bone as Sharpey's fibers. The central layer consists of an irregular feltwork of connective tissue fibers partly collagenous, partly precollagenous. It is rich in cells which are here much more numerous than in the outer layers. This central layer is the site of cell proliferation and new formation and rearrangement of fibers. For a long time these layers are of approximately the same width but as sutural growth comes to an end the central layer gradually disappears.

The development of a serrated suture can be understood if we remember that the spreading of a suture is caused by the proliferation of the sutural connective tissue and that apposition of bone at the two opposing edges is a secondary process.

Proliferation of the sutural connective tissue and apposition of bone occur simultaneously. If one were to imagine that the proliferation of connective tissue proceeded alone for a time, the bones would become separated by a wide

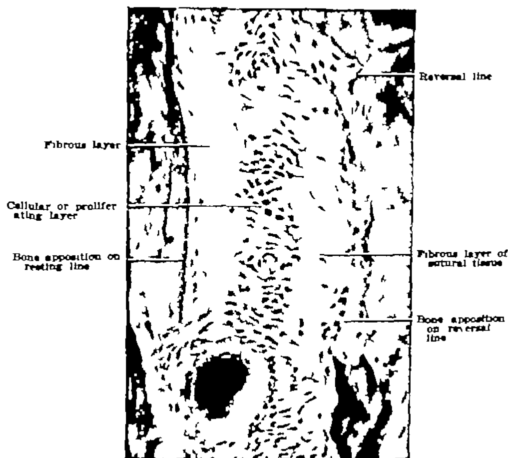


Fig. 67.—Part of the premaxillo-maxillary suture of a young rhesus monkey. Decalcified section. Hematoxylin-eosin stain. Note the division of the sutural connective tissue into three layers and the active apposition of bone on both bony surfaces. On the left side of the illustration, bone apposition occurred on a resting line; on the right side on a reversal line. (Courtesy Dr. A. G. Brodie.)

strip of connective tissue. If this were then followed by the apposition of bone in alternating small areas on the sutural edges interdigitating processes would develop. It is important to realize that this development is not, as often believed, the result of alternation of apposition and resorption on the two opposing bones but of localized apposition only. *It is true that small areas* of resorption can be found on sutural surfaces, but the areas appear on the projecting processes as well as along the grooves into which these processes fit. This irregularity of location proves that the resorption is not a part of

the development of the serrated pattern of the suture. Resorption is due rather to mechanical conditions and disturbances a fact which can be proved by the frequent occurrence of slight hemorrhages and other signs of mechanical injury in the sutures of young individuals.

Not all bones connected by a suture show an equal rate of growth. In many sutures one bone grows much faster than the other for example in the squamosal suture between the temporal and parietal bones. This results in the apparent migration of the suture Histologically such sutures are characterized by apposition of bone to one of the adjoining bones and inactivity or even resorption, of the other Sutures of this kind are generally simple, at least during the time of their migration.

Secondary Cartilaginous Growth Centers.—Development of some membranous bones is complicated by differentiation of cartilage in a later stage of their development This cartilage is not part of the primordial cartilaginous skeleton but develops secondarily as an adaptation to specific conditions. The development of such secondary cartilage and its influence upon the growth of a bone, can best be exemplified in the development of the mandible. Although here several cartilaginous parts develop only one will be described in detail namely the cartilage in the condyloid process.

The mandible develops as a membranous bone lateral to and at some distance from, Meckel s cartilage In the third month of intrauterine life the connective tissue covering the bony condyloid process differentiates into cartilage. Cartilage however develops only in the deep layer of the connective tissue and does not reach the articular surface. The cartilaginous cap takes an important part in the growth of the condyloid process, which proceeds by simultaneous growth of the cartilage and its replacement by bone in the deep layers. Although this process is analogous to that in epiphyseal and in articular cartilages of long bones the condyloid cartilage of the mandible is not homologous to either one. The condyloid cartilage cannot be called epiphyseal cartilage because it does not separate two parts of the bone nor can it be designated as articular cartilage because it does not form the *articular surface* but is always covered by a layer of fibrous or fibrocartilaginous tissue. That the condylar cartilage is itself covered by connective tissue is, moreover of great biologic importance. In contradistinction to the true articular cartilage and epiphyseal cartilage, which can thicken only by interstitial growth the condylar cartilage of the mandible grows in thickness not interstitially but by apposition from the deepest layer of its fibrous covering The realization of this difference is of the greatest importance for the understanding of the different behavior of the mandible on the one hand and of the *cranial base and long bones on the other in disturbances of growth*

The cartilage of the mandibular condyle does not disappear at the end of the growth period. At this time not only proliferation of the cartilage but also its replacement by bone cease *A terminal bony plate forms subjacent to the thin remnant of the cartilage which persists throughout life* It has to be

repeated that this cartilaginous cap is covered by a layer of dense connective tissue that forms the articular surface. The persistence of the growth cartilage in the mandible is important for the understanding of the singular behavior of this bone in acromegaly

During the development of the mandible similar centers of cartilage develop at the tip of the coronoid process and, later in the symphysis. These centers are of less importance for the growth of the mandible than the growth center in the condyle. The cartilage in the coronoid process disappears as early as the sixth intrauterine month and the cartilage in the symphysis, during the first year of postnatal life.

Cartilaginous Growth Versus Bone Growth.—It cannot be overemphasized that bones do not grow only by the growth of bone. Bone growth, that is, apposition of bone on free bony surfaces, is the primary factor in the growth of long bones in thickness Longitudinal growth of long bones, however is achieved primarily by the growth of cartilage. Even without the secondary replacement by bone, the proliferation of the cartilage increases the length of a long bone. Endochondral ossification of the proliferating epiphyseal and articular cartilages serves the growth of the diaphysis and epiphysis and thus the establishment of normal functional structure of a growing bone.

If one considers the cranium (the skull without the mandible) as a unit, its enlargement is primarily dependent (1) on cartilaginous growth, as seen for example in the spheno-occipital synchondrosis (2) on proliferation of connective tissue as seen in the sutures (3) on surface apposition of bone in many discrete areas and (4) modeling resorption. Endochondral ossification at the spheno-occipital synchondrosis and sutural apposition of bone are secondary They serve the growth of single bones and thus the establishment of the normal functional structure of the skull as a whole.

The mandible is rather comparable in its growth with a long bone because cartilaginous growth in the condyle and appositional growth of bone in other areas *combine with modeling resorption during its enlargement.*

A clear appreciation of the differences between the various mechanisms of growth of bones is imperative for an understanding of the different reactions in different parts of the skeleton under pathologic conditions, responses which at first seem to be haphazard. It is also helpful for the understanding of the coordinated features of the skeleton which distinguish certain somatic types of the human body

In the longitudinal growth of the axial and appendicular skeleton, growth of cartilage and simple appositional growth of bone from the periosteum are coordinated. However either one may be accentuated at the expense, as it were, of the other If growth of cartilage is preponderant, the bones will be long and slender and the body type will repeat the shape of the single bone. Conversely if appositional growth of bone dominates, the bones will be short and thick and so will the body

It is of great interest that the face shows an analogous variation mainly because of the participation of cartilaginous and bony growth in the shaping of the mandible The growth of the condylar cartilage is responsible for the increase of the over-all length of the mandible and of the height of its ramus Indirectly the latter determines the height of the entire face because the heightening of the ramus provides the space into which not only mandibular but also maxillary teeth erupt and alveolar processes grow

Apposition of bone at the posterior border of the ramus increases the anteroposterior diameter of the ramus and determines the degree of the mandibular angle

If cartilaginous growth dominates over surface apposition of bone the tall and slenderly built individual will also have a long face—the mandible will be long its ramus high and narrow and the mandibular angle will be obtuse. A short and stocky individual in whom surface apposition of bone dominates over growth of cartilage will have a short face—the mandible will be short, its ramus low and wide and the angle will approach a right angle.

Growth of the Skull.—The complexity of the skull, in a phylogenetic and ontogenetic and in a functional sense, is especially apparent if one tries to analyze its growth. For this reason it has taken a long time to acquire a fairly clear picture of the intricate changes in the different parts of the skull during its development and growth. The single fact that the bony capsule of the brain is inseparably linked with the masticatory facial skeleton so that these two parts of the skull are integrated into one anatomic and biologic unit, accounts for many complications. These complications arise for instance, because the growth of the capsule of the brain is entirely dependent upon that of the brain itself whereas that of the masticatory skeleton is, to a great extent dependent upon muscular influences, dentition and the growth of the tongue. These two parts of the skull not only follow different paths of development, but the timing of their growth rates is also entirely divergent. The brain has, at the age of twelve years, almost completed its growth by reaching about 90 per cent of its ultimate weight and volume. At this age, however the dentition and, therefore, the jaws are only starting their final phase of growth which ends eight or ten years later

Although the growth of any one part of the skull is coordinated to the growth of the whole it is advisable to discuss the growth of the skull under the following headings

1 Growth of the brain capsule in a strict sense. This concerns the growth of the inner plate of the bones of the cranium.

2. Growth of the cranial superstructures. The outer plates of the cranial bones, serving mechanical functions in many areas, show striking divergences from the growth of the inner laminae. These divergences are much more marked in the primitive and extinct races of mankind than in modern man.

3 Growth of the facial skeleton This shows, in many ways, independent curves in space and time An additional complication is produced by differ

ences in the mechanism of growth of the upper facial skeleton and that of the mandible.

4. Growth of the facial skeleton and tooth eruption. Here the interplay between skeletal growth and eruption and movement of teeth is to be described.

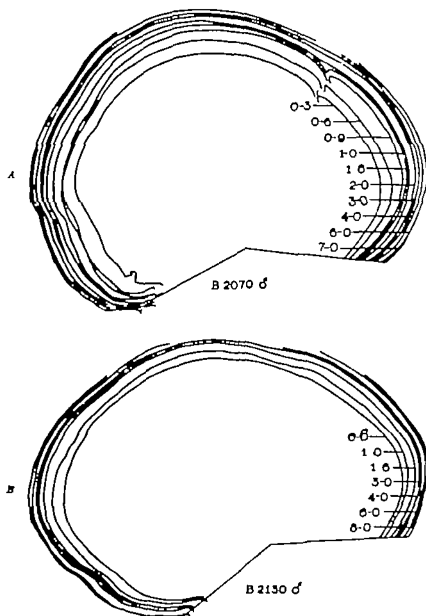


Fig. 58.—Concentric growth of the cranial vault. Superimposed outlines of the skull from craniometric roentgenograms of the same individual at different ages. (After Brodie.)
A. From three months to seven years of age.
B. From six months to eight years of age.

5. Growth of the pneumatic, or air-containing cavities of the skull. These will be discussed separately because they may expand at an age when other processes of growth have long ceased.

GROWTH OF THE BRAIN CAPSULE.—It has been mentioned before that the brain grows much more rapidly than the facial area and that by the age of twelve years the brain has reached about 90 per cent of its final volume. Already in the third or fourth year of life the rate of growth of the brain decreases considerably and with it of course that of its capsule

If roentgenograms of the same child are taken at regular intervals, it can be shown that the growth of the brain capsule is, by and large, a concentric growth (Fig 58) The cranial base is taken as the fixed point and the superposition of the pictures is done by superposing the region of the sella turcica. Much has been said about the impossibility of finding a truly fixed point of reference during the growth of the skull but the difficulties in this respect have been magnified because we are mostly concerned with relative changes of the different parts of the skull to each other It is possible to study these changes by selecting the most convenient basis for comparison. Although the cranial base grows with the growing skull it furnishes the most convenient ' fixed point for growth studies. It is, furthermore entirely reasonable to take the region of the sella and, thus, the hypophyseal region as a starting point for comparative studies because this region of the brain and of the axial skeleton seems to be truly a crucial point in the development of the vertebrates.

The mechanism of the enlargement of the cranial base on the one hand and of the cranial vault on the other have already been described. In the base it is principally growth of cartilage which lengthens and widens the diameters of the base In the cranial vault it is growth of sutural connective tissue The cartilaginous growth occurs mainly in the spheno-ethmoidal intersphenoid sphenooccipital and intraoccipital synchondroses. It is interesting to see that of the intraoccipital synchondroses those between lateral parts and squama run transversely while those between basilar part and lateral parts show an almost sagittal course. This relation between the intraoccipital sutures prepares for a widening of the occipital foramen in both anteroposterior and lateral directions (Fig 59) The intersphenoid synchondrosis disappears before or soon after birth the intraoccipital synchondrosis in the fourth and fifth years. The cartilaginous plate between occipital and sphenoidal bones, which is not entirely replaced by bone until about the eighteenth year of life (sixteenth to twentieth) is the most important of the basal growth cartilages.

The connective tissue growth initiating the expansion of the cranial vault is, of course, sutural growth It has to be realized that the ossification of the proliferating sutural connective tissue as the replacement of the proliferating cartilage by bone is but a secondary phase in the growth of the skull Apposition of bone should properly be considered as growth of the single bones of the skull Only thus can one understand the selective influence of different diseases and hereditary factors upon the growth of either the cranial base or the cranial vault

Especially in the first years of life, when the rate of growth of the skull is greatest, the changes in the curvature of the bones forming the convex vault

of the skull are significant. It is clear that these bones, in expanding have to flatten out in accordance with the increase in radius of the grow brain. Expansion occurs by sutural growth only Flattening is accompli by resorption from the inner surface in the areas close to the sutural bor and apposition of bone on the inner surface in the central areas. This res tion on the cerebral surface has been denied by some investigators. Ther however no doubt that it does take place though it seems to be active onl the first years of postnatal life. In the otic region, however apposition on outer and resorption on the inner surface of the temporal squama play a n important role in widening the brain capsule (Fig 60) Later when the r of growth of the brain decreases rapidly and when therefore, the change

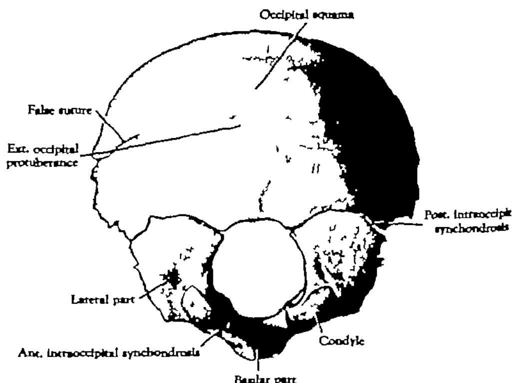


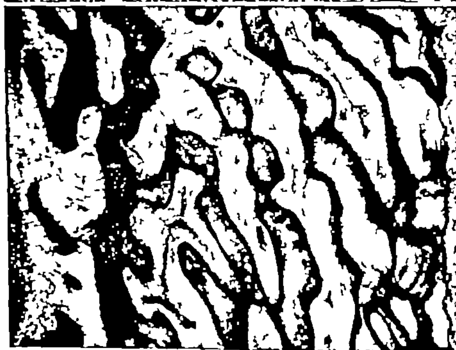
Fig. 59—Occipital bone of 1 year-old child. (Tandler)

curvature is only slight, this change is brought about solely by different apposition. Then, apposition on the cerebral surfaces in the central areas of t bones and increased apposition on the external surfaces in the marginal are suffice to bring about the slight changes leading to a flattening of the bon

The concomitant thickening of the bones of the cranial vault occurs apposition on both surfaces of the bones except during the early period wh restricted resorption can be observed in the border areas of the single bon It is especially noteworthy that on the inner surface of the bones of the sk (and this is valid not only for the bones of the cranial vault, but also for tho forming the cranial base) apposition of bone predominates. This is the be

A





B

Fig. 60.—Frontal section through the temporal squama of a newborn infant. Note the signs of resorption on the cerebral surface and signs of apposition on the periosteal surface of the bone.

A, General view.

B, High magnification of the area between the two lines in *A*.

possible proof that the enlargement of the cranial capacity occurs by s growth. This sutural growth initiated by proliferation of the sutur nective tissue and followed by apposition of bone at the sutural bord even greater than is necessary to accommodate the growing brain, an allows, at the same time for the apposition of bone on the cerebral surf the cranial bones.

The continual apposition of bone on the inner surfaces of the cran sule is said to progress even after sutural growth has ceased, slightly re the cranial cavity It is claimed that this is due to a 'shrinkage' of th during its maturation. It is known that the specific gravity of the br creases after it has reached its ultimate volume and this may be ass with a slight decrease in the volume. It is, however more probable that s growth continues after brain and cranial cavity have reached their final v Sutural growth at that time would provide space for the strengthening cranial walls by internal apposition without reducing the cranial ca

In view of the fact that, with the exception of the temporal squan cerebral surfaces of the bones of the skull after the first years of life sh position only it should be realized that the gradual deepening of vascular g and the development of the digital impressions are not due to a hollowing the grooves but to a heightening of their borders.

Growth of the Cranial Superstructures.—The thickening of the c bones is not uniform. In many regions a progressive divergence develo tween the inner plate the brain capsule in a stricter sense and the plate which is largely under mechanical influences. These diver are found, for instance, in the nuchal region where the nuchal crests and cially the external occipital protuberance develop under the influence posterior musculature of the neck. Such a divergence between the two of the cranial bones is most pronounced, however in two regions the s orbital and the otic and mastoid areas.

At birth, the outer and inner plates of the frontal bone are parallel, a s orbital ridge does not exist, and the frontal sinus is absent (Fig 61) the outer plate in the supraorbital region grows at a greater rate than the plate by apposition on the outer surface so that it seems to bend away the inner plate, forming a blunt ridge above the upper border of the o entrance. At first, spongy bone and, later the frontal sinus occupy the between the internal and the external plates of the frontal bone. It is h probable that this accentuation of the outer plate in this region occurs response to the growing masticatory forces which are transmitted to the anterior part of the cranial base by the frontal processes of the maxilla the frontosphenoid processes of the zygomatic bones.

These changes explain the difference in the external shape of the head in the child and in the adult. The forehead is high and bulging i infant and more sloping or receding in the adult. These changes do not adv as far in the female as in the male which accounts for the "infantile" sha the female skull.

The changes in the mastoid region are even more striking In the new born infant the lack of any superstructure in this part of the skull is evident from the following facts

1. The mastoid process has not yet started to develop

2. The stylomastoid foramen lies unprotected on the lateral surface of the skull because of the absence of the mastoid process. This explains injuries to the facial nerve, for instance, during forceps delivery

3 The articular fossa faces almost entirely laterally and only slightly downward instead of being horizontal as in the adult. An articular eminence is not yet present.

4. The bony part of the external auditory meatus is absent because the tympanic bone is represented by a bony ring only

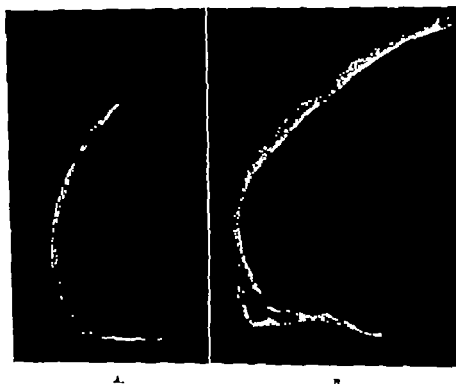


Fig. 61—Sagittal sections through the frontal bone at the approximal level of the trochlear groove.

A Newborn infant.

B Young adult.

Note the growing divergence between inner and outer plates of frontal bone in the supraorbital region and the development of the frontal sinus in the space between the two plates.

The changes in this region start soon after birth and are well advanced in the second year of life (Fig. 62) They are the same in principle as those described in the supraorbital area. By accentuated apposition of bone above the tympanic membrane extending anteriorly to the root of the zygomatic process and posteriorly onto the mastoid plate the outer and inner laminae of the temporal bone are gradually folded. At the same time resorption on the

cerebral surface of the temporal squama widens the cranial cavity in this area (Fig 60) By this remodeling the originally oblique outer plate in this region is divided into an upper almost vertical, and a lower horizontal part. In the

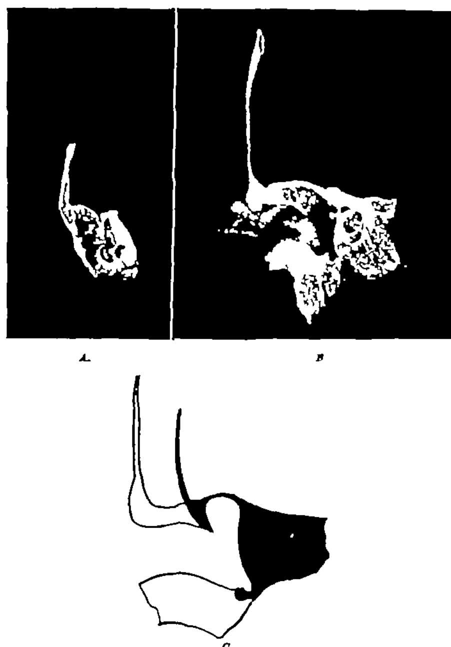


Fig. 62.—Frontal sections through the temporal bone at the level of the center of the external acoustic meatus

A Newborn infant.

B Adult

C Diagrammatic superposition of *A* and *B* the newborn infant in black, the adult in outline The broken line represents the position of the tympanic membrane.

most anterior region this leads to a change in the position of the articular surface for the mandible which gradually shifts into a horizontal plane At the same time the articular eminence develops. It is clear that this change coincides

with the beginning of the masticatory function and that it contributes in the first two years of life to the "downward shift" of the mandible and thus to the developing of an intermaxillary space (Fig 63)

In the tympanic region the remodeling of the bony plates leads to the development of the roof of the bony part of the external auditory meatus, the floor of which develops simultaneously by the growth of the tympanic bone. This bone at first a C-shaped ring changes into an almost closed bony tube In the course of this change of the tympanic ring to the tympanic bone a defect persists for a few years in the floor of the bony acoustic meatus. Remnants of this defect, which normally closes in the third year of life persist in almost 20 per cent of adult skulls and should not be confused with a traumatic defect

In the mastoid region the "folding" of the plates of the temporal bone is coincident with the outgrowth of the cone-shaped mastoid process which develops on the lateral side of the stylomastoid foramen. This foramen moves simultaneously to the base of the skull and thus the facial nerve is safely protected from injury The development of the mastoid process is correlated to the acquisition of the upright posture and gait and provides the necessary area of attachment for the sternocleidomastoid muscle, a function of which is to balance the head.

Growth of the Facial Skeleton.—The growth curve of the facial skeleton is widely different from that of the neurocranium. At birth, the latter overshadows the former because of the advanced development of the brain and the lack of function of the masticatory apparatus. It has been pointed out that the brain and with it its capsule, triples its volume in the first two years of life and then slows down in its growth until, after the seventh year of life, the annual increment is almost negligible. After the first year of life the facial skeleton not only grows faster than the brain case, but also retains a considerable rate of growth far longer These differences are easily visualized in comparing the head of an infant with that of an adult. The bulging forehead of the former the receding forehead of the latter the insignificance of the maxillary and mandibular skeleton in the infant and their more or less prominent position in the adult are the external expressions of the different tempo of growth of these two main parts of the skull

During the growth period the facial skeleton increases in all three dimensions of space—in height, width, and depth. The detailed mechanism by which the coordination and simultaneity of the enlargement of the face in the three planes are achieved is one of the fascinating chapters of biology Before going into the details, however one point has to be stressed namely the regularity of this process of growth or the maintenance of the original pattern of the facial skeleton and its relations to the skull. It is known, for instance by the study of carefully made roentgenograms of the same child at different ages, that the plane of the palate the occlusal plane and the plane of the lower mandibular border maintain a fairly constant angular relation to the base of the skull. In other words, during the growth of the facial skeleton, these structures and planes each shift roughly parallel to themselves.

During the growth of the skeleton of the upper face, the central problem is the shift and enlargement of the maxillary complex that is, maxilla and palatine bone. In part, the enlargement of the maxillary skeleton in an anteroposterior diameter is simultaneous with the growth of the base of



A.



B

Fig. 61.—Four stages in the development of the temporal bone.
A. Newborn infant.
B One-year-old child.
C Four year-old child.
D Adult.
Note the absence of a mastoid process in the newborn infant. Note th changes of the tympanic ring of the newborn infant to the tympanic bone of the adult. The inferoa terior wall of the tympanic bone shows a defect in *C* which closes in the fifth year of life but may persist in the adult. Note the change in the position of the articula fossa and the gradual development of an articula tubercle.

the skull in the same dimension. This growth, however is achieved only to a small degree in that part of the base which is anterior to the spheno-occipital synchondrosis. Since the latter is situated behind the area of at tachment of the facial to the cranial skeleton growth in this location will *affect more the relations of the facial skeleton to the neurocranium* than the absolute growth of the face.

The more important sites of growth for the maxillary complex are three sutures on each side the frontomaxillary suture between the frontal bone and

frontal process of the maxilla the zygomaticomaxillary suture between maxilla and the zygomatic bone (and secondarily the zygomaticotemporal ure in the zygomatic arch) and the pterygopalatine suture between the rygoid process of the sphenoid bone and the pyramidal process of the atine bone (Fig 64) It is significant that these three sutures are parallel



C



D

Fig. 63.—(For complete legends see opposite page)

o each other and are all directed from above and anteriorly downward and osteriorly Growth in these sutures will have the effect of shifting the naxillary complex downward and anteriorly

Growth in the described sutures increases height and length or depth hat is, the vertical and anteroposterior dimensions, of the nasal parts of the

maxillae and palatine bones only The subnasal part of the maxilla increases in height by apposition of bone on the free borders of the alveolar process simultaneously with the eruption of the teeth. In an average skull sutural growth contributes more to the increase in depth growth on the alveolar border more to the increase in height In other words, sutural growth contributes more to the forward shift growth at the alveolar border contributes more to the downward shift of the upper jaw

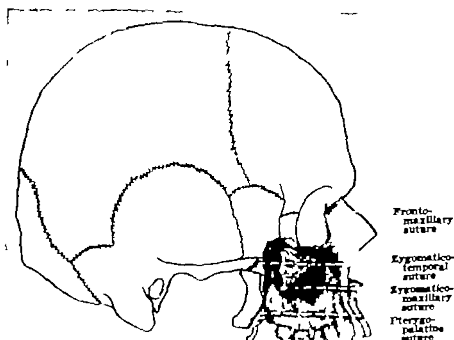


Fig. 64.—The sutural sites of maxillary growth (red) Photograph of the maxilla of a sixteen-year-old boy in the diagrammatic outline of a skull. Note the arrangement of the frontomaxillary zygomaticomaxillary zygomaticotemporal, and pterygopalatine sutures in the same inclination from above, downward, and backward.

At the same time regulatory bone apposition and modeling resorption take place Sutural growth alone evidently does not suffice to achieve the normal height of the nasal cavity at the same time the orbits, nearly of final size at birth, would gain too much in height by the growth at the sutures between frontal bone and zygomatic and maxillary bones. As a correcting process, apposition of bone can be observed on the orbital floor (Fig 65) resorption on the nasal floor The latter is in turn compensated by apposition on the oral surface of the palate (Figs. 66 and 67) Thus the palate "shifts" downward by the additive effect of sutural growth and of continued rebuilding The apposition of bone at the orbital floor is also proof for the reality of sutural growth.

The downward and forward growth of the subnasal part of the maxillary body is accompanied by intensive apposition of bone at the free borders of the alveolar process. The apposition in this area not only contributes to the increase in height of the upper facial skeleton, but also allows for proper adjustment of the alveolar process and the dental arch to the teeth, especially during

the eruption of the permanent dentition During this time of change in the proportionate size of the members of the two dentitions such an adjustment is especially necessary At the same time the growth of the alveolar process



Fig. 43.—Section through the orbital floor of a child nine months old. Note the layer of osteoblasts and the seam of osteoid tissue denoting rapid appositional growth.

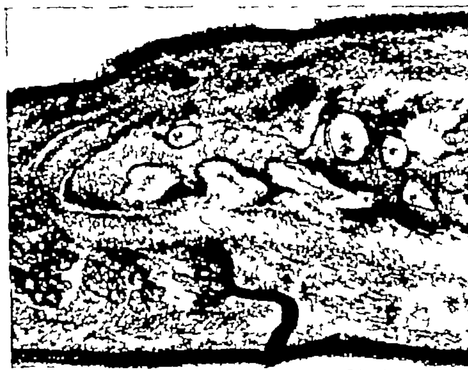


Fig. 44.—Section through the posterior end of the hard palate of a human fetus of the seventh month. Note the resorption of bone on the nasal surfaces and apposition of bone on the oral surfaces of the trabeculae and apposition of bone at the posterior margin.

accounts for transition from the flat curve of the *infantile* to the more highly arched curve of the adult palate The downward shift of the hard palate by resorption on its nasal surface and by apposition on its oral surface *tends to*

obscure the downward growth of the alveolar process. The palate maintains a position to the alveolar process that allows the most efficient buttressing of the dental arches by the pterygoid processes that, in turn, are correlated in their downward growth to the downward shift of the hard palate

If the described phenomena explain the vertical and anteroposterior growth of the maxillary complex, the increase in transverse diameter especially of the nasal part, has still to be accounted for It is relatively slight in the anterior parts of the maxillary skeleton which are so to speak, shifted bodily and undergo only minor adjusting changes by local apposition and resorption for example



Fig. 67—Section through the hard palate of a child nine months old. Not the resorption on the nasal surfaces and apposition on the oral surfaces of the two bony plates that form the hard palate

on the surfaces of the growing alveolar processes. The widening of the maxillary skeleton in its posterior parts, coincident with its growth in anteroposterior diameter (that is, the divergence posteriorly of the basal bone anchoring the dental arches) presents a problem because of the junction of the maxillary complex to the pterygoid processes of the sphenoid bone. Although the median palatine suture provides a site of growth increasing the transverse diameter the pterygoid processes are but a part of the unpaired sphenoid bone The adjustment of maxillary and interpterygoid width is achieved by the downward divergence of the pterygoid processes. The growth of the pterygoid processes in postnatal life occurs by apposition at the free borders and surfaces and by

corresponding modeling resorption Due to the downward divergence of these processes their increase in length by apposition at their lower ends will necessarily increase the distance of their inferior ends from one another It is interesting that the distance of the upper ends of these processes from each other a distance which equals twice the width of the upper border of the nasal choanae increases only slightly after birth, an increase which can easily be accounted for by resorptive processes in this region.

It is evident that growth in the median palatine suture is simultaneous with and correlated to the widening of the downward shifting maxillary complex. It is, furthermore apparent that growth occurs in all the other sutures of the facial skeleton, as, for instance between ethmoid zygomatic, lacrimal and nasal bones and those in contact with them.

The widening of the nasal cavities, especially of their lower part lags for quite some time behind that of the dental arches. In children the bilateral width of the posterior part of the maxillae is relatively much greater than the distance between the lower ends of the pterygoid processes. This incongruence of lower nasal width and width of the developing alveolar processes is expressed in a lateral shift of the developing molars and thus a lateral bulging of the maxillary tuber With the downgrowth of the maxillae the downward shift of the hard palate the lengthening of the divergent pterygoid processes, and the widening of the nasal cavity the posterior end of the alveolar process is more and more brought in line with the lower end of the pterygoid process. Since this alignment is proportionate to the vertical growth of the upper face the posterior end of the alveolar process and the pterygoid process coincide more in individuals with a high face (leptoprosope type) than in those with a low face (euryprosope type)

During all these changes, however the junction between maxillary body and pterygoid process, mediated by the interposed pyramidal process of the palatine bone, remains unchanged in its relations at the inferomedial corner of the maxillary tuber

The growth of the upper facial skeleton is obviously closely correlated to that of the mandible Mandibular growth can even be considered the leading factor of facial growth.

The mechanism of mandibular growth is entirely different from that of the maxillary part of the face In the latter the growth is primarily sutural initiated by proliferation of sutural connective tissue In the mandible however the main growth center is the hyaline cartilage in its condyle That the chief factor of growth is the interstitial growth of connective tissue in the upper facial skeleton but appositional growth of cartilage in the mandible, explains a certain independence of the growth of these two parts of the facial skeleton and their different reaction in certain pathologic conditions.

At birth, the mandible still consists of two halves, separated in the midline by the symphyseal cartilage and connective tissue in which the mental bones develop This suturelike junction does not seem to play any significant role

as a site of growth in postnatal life. Although the mandible develops as a membrane bone, lateral to and at some distance from Meckel's cartilage, secondary centers of hyaline cartilage differentiate in the growing mandible to take an important part in its growth. Whereas the secondary cartilage at the tip of the coronoid process disappears long before birth the cartilage in the condyle persists as the most important growth center of the mandible The secondary differentiation of a condylar cartilage is evidently an adaptation to growth of the mandible at a site of pressure namely at the articular end. It is a well-established fact that a bony surface does not grow if it is under direct pressure

The condylar cartilage cannot be compared with an articular cartilage of long bones, or with an epiphyseal plate even though growth of the mandible does occur in the condyle by proliferation of the cartilage and its gradual replacement by bone just as in the cartilages of long bones the hyaline cartilage of the mandibular condyle is covered by a thick layer of dense connective tissue whereas the articular cartilage of other bones has no covering This covering of connective tissue enables the hyaline cartilage in the condyle of the mandible to increase in thickness by appositional growth, whereas the cartilages, both articular and epiphyseal of long bones thicken by interstitial growth. The hyaline cartilage in the head of the mandible therefore holds a unique position and differs widely from that of other cartilaginous growth centers in its reaction to certain pathologic conditions (Fig 68)

Proliferation of the condylar cartilage contributes both to the increase of the mandibular ramus in height and to the increase of the over-all length of the mandible. The latter can be measured either by taking the distance between condyle and chin point gnathion, or by measuring the distance from the gnathion to a point where a perpendicular tangent to the posterior surface of the condyle meets the gnathion gonion line. Condylar growth has thus double effect because the condyle is obliquely implanted upon the body of the mandible by the obliquely ascending ramus.

Condylar growth increases the over all length of the mandible but not the length of the mandibular body nor does condylar growth contribute to the necessary increase of the anteroposterior width of the ramus itself. Here appositional growth along the entire posterior border of the ramus is the mechanism for adjusting the width of the ramus and the length of the body to the growing height of the ramus. Appositional growth at the tip and upper border of the coronoid process keeps pace with the increase in height of the ramus. At the same time resorption along the anterior border of the coronoid process and the ramus corrects the anteroposterior dimension of the ramus and lengthens the alveolar space distally

The height of the mandibular body measured from the lower border of the mandible to the free border of the alveolar process, increases almost exclusively by apposition of bone at the free borders of the alveolar process.

Growth at the condyle which rests against the articular fossa at the cranial base causes a downward and forward shift of the entire mandible. In the

first two years of life the changes in the otic region of the temporal bone (see p 101) contribute to the shift by which the lower teeth and alveolar process are more and more removed from those of the maxilla Into the intermaxillary space thus opened grow both upper and lower alveolar processes with the erupting teeth

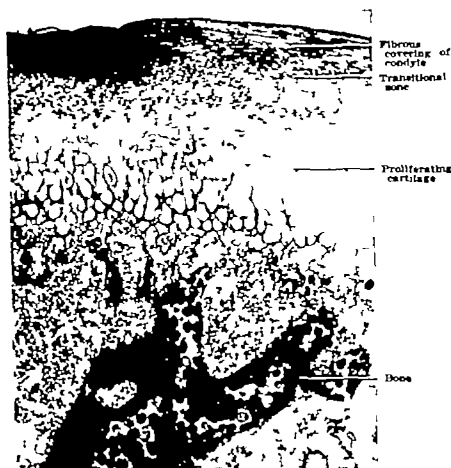


Fig. 68 —Section through the mandibul r condyle of newborn inf t. Note the fibrous covering of the hyaline cartilage and the appositional growth of the cartilage from the deepest layer of the connecti tissue. In the deep layers of the cartilage note the swelling of the chondrocytes nd the resorption f the calcified cartilage and replacement by bone. (From Orban Oral Histology and Embryology)

Apposition of bone at the lower mandibular border and in the region of the chin serves not so much the enlargement as the reinforcement and modeling of the lower jaw Changes in the shape of the alveolar process, especially during the replacement of the deciduous by the permanent teeth, occur during the vertical growth of the alveolar process. It is therefore incorrect to visualize the adaptation as a change of the deciduous arches in a horizontal plane. Instead, the permanent arches are entirely new formations adjusting to the permanent dentition during their vertical growth.

Serial roentgenograms have shown that the contour of the mandibular angle does not appreciably change during growth (Fig 69) This observation

seems to be in contradiction to the often repeated assertion that the mandibular angle decreases during the period of growth. In reality there is merely a confusing usage of the term mandibular angle and the method of measuring it. Anthropologically the mandibular angle is measured by placing the mandible on a table *to which a hinged leaf is fastened. This leaf is placed in such a position* that it touches the posterior border of the mandibular ramus at two points, one near the condyle and the other near the mandibular angle (Fig 70 *B*) The inclination of the movable leaf to the table is then measured and is termed the mandibular angle. While the mandibular angle of the anthropologists is a geometrical construction, the same term mandibular angle as used in descriptive anatomy signifies the region where body and ramus of the mandible join, a

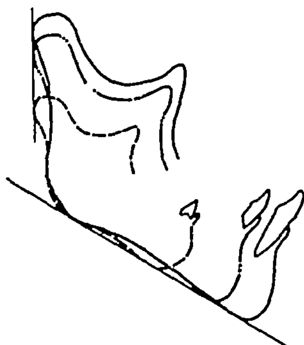


Fig. 69 —Superposition of the outlines of the mandible in three stages of growth. Note the stability of the contour of the gonial angle and the difference in the inclination of the condylar process to the lower border of the mandible. (After Brodie.)

region with a definite shape and contour The *confusion of definitions can be* easily eliminated by terming the angular region gonial angle, while the anthropological angle is termed the condylar angle. It is significant for the stability of the pattern during growth that the gonial angle remains fairly constant, but it is equally significant, for an understanding of the changes in direction of growth and mechanics of the masticatory apparatus, that the condylar angle decreases during the period of growth.

The changes in the size of condylar angle are caused by a change in the direction of the proliferation of the condylar cartilage In the first years of life the direction of proliferation is inclined more than in later years. This means that in the first phase of growth during which the length of the dental

arch increases rapidly the mandible grows more in length than in height In the second period of growth the face continues to grow in height after the length of the dental arch has almost been established. This pattern of growth finds its expression in the gradual diminishing of the condylar angle that is extremely obtuse at birth and in infancy

Since the two halves of the mandible diverge posteriorly, the growth of the mandible in its anteroposterior diameter is necessarily associated with an increase in transverse diameter or intercondylar distance.

The growth of the mandible at the condylar cartilage is indispensable for the normal vertical growth of the upper face Growth at the condyle moves the mandibular body forward and downward and thus opens the space below the cranial base into which mandibular and maxillary alveolar processes grow and the teeth erupt. Disorders of mandibular growth lead therefore secondarily to changes in the upper face They involve in the majority of individuals only the subnasal part of the maxilla.

After loss of all teeth, especially if no denture is worn, the condylar angle widens again. This change is often referred to as a senile change. It is, however not the age of the individual but the loss of function which plays the decisive role in other words, the change is to be defined as disuse atrophy The atrophy in the region of the masticatory musculature at the lower and posterior border of the gonial area leads not only to a widening of the condylar angle but also to a radical change of the bony outline and thus to a change of the gonial angle.

Growth of the Facial Skeleton and Tooth Eruption.—The correlation of teeth and jaws has often been interpreted as indicating that the presence of teeth in a proper number and relation is necessary for the normal growth of the jawbones. This assumption is erroneous. In many animals it can be observed that the development of the teeth and that of the jaws are highly independent. The same independence in man can be proved by examining cases of anodontia in which, in spite of a total lack of teeth, the jaws develop to a fairly normal size. It is, however true that development and growth of the alveolar processes are dependent on the development and eruption of the teeth. Not only does no alveolar process, in the strict sense of the word, develop if a tooth or teeth are absent but the alveolar process also disappears if teeth are lost.

While the dependence of bone growth upon the development of teeth is slight, the reverse relation that is, the dependence of tooth development and, especially tooth eruption upon growth of bone and bones, is considerable The influence of the growth of the facial skeleton upon the eruption *of teeth* is threefold (1) The growth of the maxilla and mandible, in an anteroposterior direction, provides the space necessary for the successive eruption of the posterior teeth. (2) The growth of the maxilla and mandible in height, initiated by the vertical growth of the mandibular ramus, is necessary for the free vertical eruption of the teeth. (3) Growth of bone tissue in the maxilla and mandible is one of the forces of eruption.

seems to be in contradiction to the often repeated assertion that the mandibular angle decreases during the period of growth. In reality there is merely a confusing usage of the term "mandibular angle" and the method of measuring it. Anthropologically the mandibular angle is measured by placing the mandible on a table to which a hinged leaf is fastened. This leaf is placed in such a position that it touches the posterior border of the mandibular ramus at two points, one near the condyle and the other near the mandibular angle (Fig 70 B). The inclination of the movable leaf to the table is then measured and is termed the mandibular angle. While the mandibular angle of the anthropologists is a geometrical construction, the same term mandibular angle as used in descriptive anatomy signifies the region where body and ramus of the mandible join, a

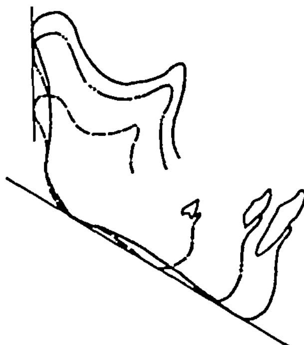


Fig. 69.—Superposition of the outlines of the mandible in three stages of growth. Note the stability of the contour of the gonial angle and the difference in the inclination of the condylar process to the lower border of the mandible. (After Brodie.)

region with a definite shape and contour. The confusion of definitions can be easily eliminated by terming the angular region gonial angle, while the anthropological angle is termed the condylar angle. It is significant for the stability of the pattern during growth that the gonial angle remains fairly constant but it is equally significant for an understanding of the changes in direction of growth and mechanics of the masticatory apparatus, that the condylar angle decreases during the period of growth.

The changes in the size of condylar angle are caused by a change in the direction of the proliferation of the condylar cartilage. In the first years of life the direction of proliferation is inclined more than in later years. This means that in the first phase of growth during which the length of the dental

arch increases rapidly the mandible grows more in length than in height In the second period of growth the face continues to grow in height after the length of the dental arch has almost been established This pattern of growth finds its expression in the gradual diminishing of the condylar angle that is extremely obtuse at birth and in infancy

Since the two halves of the mandible diverge posteriorly, the growth of the mandible in its anteroposterior diameter is necessarily associated with an increase in transverse diameter or intercondylar distance.

The growth of the mandible at the condylar cartilage is indispensable for the normal vertical growth of the upper face Growth at the condyle moves the mandibular body forward and downward and thus opens the space below the cranial base into which mandibular and maxillary alveolar processes grow and the teeth erupt Disorders of mandibular growth lead therefore secondarily to changes in the upper face They involve in the majority of individuals only the subnasal part of the maxilla

After loss of all teeth especially if no denture is worn, the condylar angle widens again. This change is often referred to as a senile change It is, however not the age of the individual but the loss of function which plays the decisive role In other words, the change is to be defined as disuse atrophy The atrophy in the region of the masticatory musculature at the lower and posterior border of the gonial area leads not only to a widening of the condylar angle but also to a radical change of the bony outline and thus to a change of the gonial angle.

Growth of the Facial Skeleton and Tooth Eruption —The correlation of teeth and jaws has often been interpreted as indicating that the presence of teeth in a proper number and relation is necessary for the normal growth of the jawbones. This assumption is erroneous. In many animals it can be observed that the development of the teeth and that of the jaws are highly independent. The same independence in man can be proved by examining cases of anodontia in which, in spite of a total lack of teeth the jaws develop to a fairly normal size It is, however true that development and growth of the alveolar processes are dependent on the development and eruption of the teeth. Not only does no alveolar process, in the strict sense of the word, develop if a tooth or teeth are absent, but the alveolar process also disappears if teeth are lost.

While the dependence of bone growth upon the development of teeth is slight, the reverse relation, that is, the dependence of tooth development and especially tooth eruption upon growth of bone and bones, is considerable The influence of the growth of the facial skeleton upon the eruption of teeth is threefold (1) The growth of the maxilla and mandible, in an anteroposterior direction, provides the space necessary for the successive eruption of the posterior teeth. (2) The growth of the maxilla and mandible in height, initiated by the vertical growth of the mandibular ramus, is necessary for the free vertical eruption of the teeth. (3) Growth of bone tissue in the maxilla and mandible is one of the "forces of eruption.

The correlation of anteroposterior growth of the jaws and eruption of the teeth can best be observed in studying the position and movement of the permanent molars during their eruption. In a child of three years, for instance, the jaws are just long enough to accommodate the deciduous teeth. The first

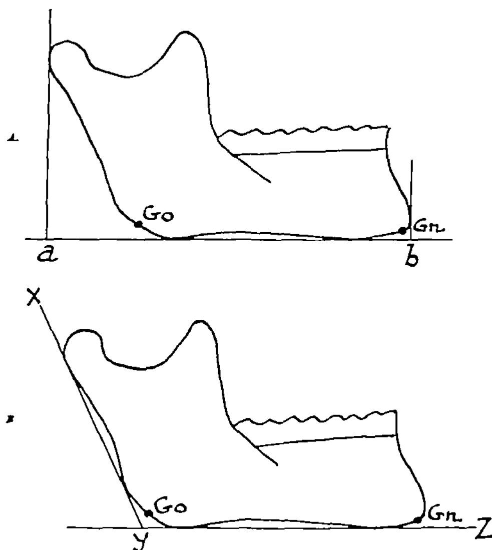


Fig. 70—Four diagrams to illustrat growth of the mandible.

A Diagrammatic outline of the mandible *G* gnathion *Go* gonion *ab* over-all length of the mand ble

B Outline of a mandible t *xyz* condylar angle.

C Superposition of the diagrammatic outline of an i fantil and an adult mandible. The condylar angle *xy* of the child decreases to *x'yz* of the ad lt.

D Outlin of an infantil and an adult mandibl superposed on the gnathion t show the increments of the ramus due t cartilaginous condylar growth (stippled) an appositional bone growth (hatched)

permanent molars, already far advanced in their development at this time, are found in the maxillary tuber and in the root of the mandibular ramus. The occlusal surface of the upper molar faces backward and downward that of the lower face f rward and upward. During the succeeding years these

teeth undergo movements which place their crowns in the right plane that is, their occlusal surfaces become parallel to those of the deciduous teeth. These rotatory movements are possible only because the upper and lower jaws lengthen to such an extent that sufficient space is created behind the last deciduous teeth to receive the first permanent molars. The same process repeats

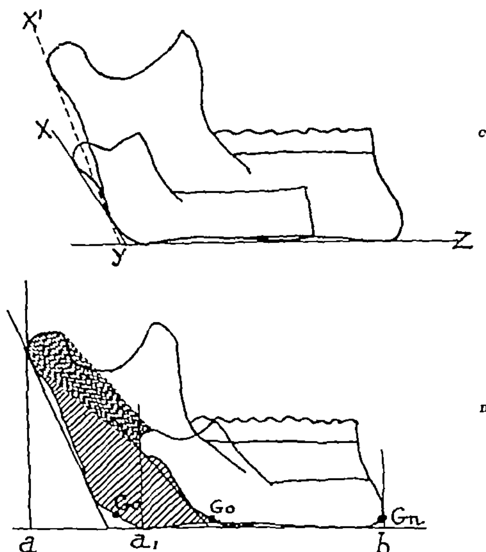


Fig. 70.—(For complete legend see opposite page.)

itself after the sixth year of life when the second molars undergo the last phases of crown development and go through the same rotatory movements as did the first molars. The same correlated changes occur for the third time prior to the eruption of the third molars.

During this last phase of molar eruption, disturbances in the correlation between the growth of the jaws and the eruption of the third molars occur rather frequently. The primary reason for this seems to be that the third molars in modern man are rudimentary and consequently vary greatly in

shape and size Not infrequently one or more of the four third molars are absent. Another consequence of this phylogenetic change is the often delayed development and eruption of the third molars and the great variability in the time of their eruption.

The loss of the third molar, and thus the reduction of the dentition in length is but one phase in the reduction of the masticatory apparatus in the phylogenesis of man. The second phase is the reduction of the facial skeleton most strikingly expressed in the gradual decrease of facial protrusion. The reduction in length of the jaws and the reduction of the dentition are not entirely correlated. This leads to frequent disharmony between length of the jaws in an anteroposterior direction and length of the dental arch. It seems that the shortening of the jaws is, in modern man already further advanced and more firmly established than the shortening of the dental arch. This reduction of space for the third molars is enhanced in many individuals by the fact that the third molars erupt at a time when the general growth of the body and that of the jaws is nearly completed.

The frequent impaction or even embedding of the third molars is thus easily understood. There remains only to be explained the fact that the lower third molar is so much more frequently affected by this discordance between bone growth and tooth development than the upper third molar The pre eruptive position of these two teeth gives the clue to their different behavior The upper third molar developing in the maxillary tuber faces downward and backward. If growth of the maxilla at its posterior end is inadequate, the rotation of the third molar into its proper position will be inhibited. This tooth if it continues its eruptive movement in the direction of its long axis, will not encounter any obstacle and will erupt though in a more or less abnormal axial position.

The lower third molar faces upward and forward during its development. If sufficient space for its pre-eruptive rotation is not provided, and if it starts to erupt in the direction of its anteriorly inclined long axis, its crown moves toward the root or crown of the second molar and is, sooner or later arrested in its movement.

The space for the vertical growth of the alveolar processes and for the vertical eruption of the teeth is extended by the growth in height of the mandibular ramus. In this way the body of the mandible is moved away from the level of the cranial base and the maxilla and the mandible grow toward each other The different rate of growth of the mandibular condyle is responsible for the different rate of vertical eruption under varying conditions. Thus, inhibition of this growth, as in mandibular retrusion, causes an under eruption of the molars and bicuspids. In mandibular protrusion, in which the mandibular ramus is too high the teeth are overerupted.

The influence of growth of bone tissue in contrast to growth of the facial bones, upon the eruption of teeth can be understood only by analyzing the *process of eruption. In such an analysis the meaning of the term* eruption should be extended beyond that phase in which the teeth cut the gums.

he term eruption should also include all the movements of the teeth which receede their actual emergence into the oral cavity Furthermore, it should e realized that the movements of the teeth do not cease when the teeth estab sh occlusal contact with their antagonists It is known that eruption in an xial direction continues throughout the life of the teeth and that it is com ined with other movements of the teeth such as the mesial drift toward the idline in man.

Eruption in a wider sense is the result of differential growth between the eeth and the surrounding bone. In the first phases, growth of the teeth is bvious in the later phases, growth of the tooth is restricted to the continual pposition of cementum.



Fig. 71 —Cushioned hammock ligament. Root end of an erupting lower cuspid (canine) Note the numerous fluid-containing tissue spaces in the ligament. (Sicher.)

Eruption may be divided into two phases The first, the prefunctional phase, starts with the development of the root and ends when occlusal contact is established The second, or functional, phase continues from then on indefinitely During the first phase, growth of the tooth itself plays the dominant role in its axial movement. It is the proliferation of the pulpal connective tissue which generates the slight pressure necessary for the movement. This pressure is directed toward the surface of the jaws by the presence of a ligament upon which the growing end of the root rests (Fig 71) This hammock ligament is anchored in the bone of the primary socket, or better crypt of the tooth and consists of collagenous fibers between which great

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quantities of fluid are found The ligament suspends the tooth and protects the bone in the fundus of the crypt from resorption resulting from the pressure of the growing root and permits a movement of the tooth only toward the surface of the jaw instead of growth of the root into the jaw itself

Even the axial movement of an erupting tooth cannot, in many instances, be entirely accounted for by growth of its root. The tips of the crowns of some teeth travel a distance that is greater than the length of their roots. This means that another factor is active during the axial eruption. Most of the erupting teeth undergo other intricate movements besides the axial movement, such as rotation around a transverse axis as in the molars, or rotation around their long axis, as in permanent incisors. Finally, some teeth move bodily during eruption such as an upper permanent incisor which has erupted lingually from its deciduous predecessor These movements which may be termed tilting, rotating and drifting movements, respectively can be explained only by the influence of surrounding tissue upon the tooth. In reality it is growth of bone preceded by the growth of osteogenic connective tissue in distinct and limited areas which brings about the necessary changes in the position of the erupting tooth. Growth of bone at the fundus of the crypt accounts for an axial movement of the growing tooth so that growth of the tooth itself and growth of the bone, apically to its root end, produce the sum of the axial movement (Fig 72) This is the reason that the crown of a tooth may travel a greater distance than could be accounted for by the growth of its root alone. The large amount of fluid in the hammock ligament acts as a hydraulic cushion, distributing evenly the slight pressure exerted by the growing bone on the growing root end. At the same time its presence increases the incompressibility of the tissue intervening between the growing bone and the growing root. In this way the growing bone is prevented from encroaching upon the growing root.

During all other movements of an erupting tooth tilting rotating and drifting movements, apposition of bone behind the moving tooth and resorption of bone in front of it can easily be observed. It is, however, the apposition in certain restricted areas which is the primary moving agent. As long as the crown of a tooth is embedded in the jaw and situated in the wide bony crypt, the connective tissue between the bone and the reduced enamel epithelium covering the crown is rich in fluid which is contained in rounded tissue spaces (Fig 73) The function of this fluid is to render the connective tissue surrounding the crown incompressible and thus to transmit the pressure exerted by the growing bone evenly and undiminished, to the tooth. By the movement of the tooth, thus induced, the pressure is exerted upon the bone in the direction of the movement, and resorption of the bone in this area provides the necessary space.

The movements of a tooth do not stop when it has reached the occlusal plane During the second or functional, phase of tooth eruption these movements are also the result of differential growth between the tooth and the surrounding bone It is the different growth pattern of cementum and bone

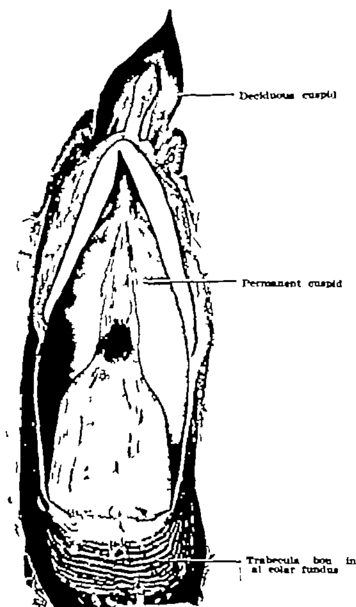
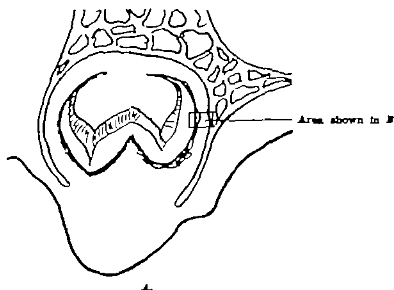
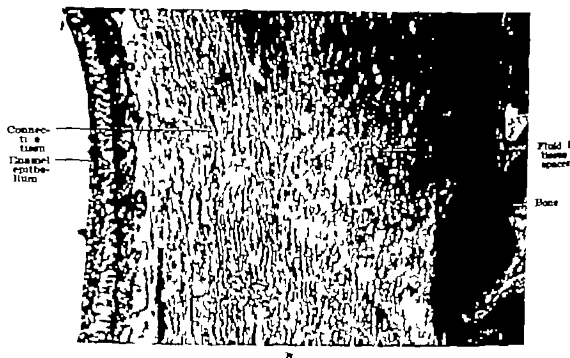


Fig. 2.—Longitudinal section through the mandibular cuspid (canine). The deciduous tooth is about to be shed. Note the trabecular bone at the al eolar fundus. (Magnification ×4½.) (R. Kronfeld.)



A.



B

Fig. 72.—Upper first deciduous molar of a four-month-old child.
A Lateral view in diagrammatic outline.
B Pericoronal cushioned connective tissue. (Original magnification ×125 reduced to [illegible])

which results in movement of a tooth. Normally the cementum grows throughout life, by apposition on its entire surface. The rate of apposition of cementum varies in different areas. It is greatest in the apical region of the root, thus lengthening the root and partly compensating for the loss of tooth substance by attrition of the incisal edge or occlusal surface. The continual growth of cementum is responsible for the continual presence of a thin layer of cementoid tissue on the entire root surface. Cementoid tissue, the uncalcified cementum

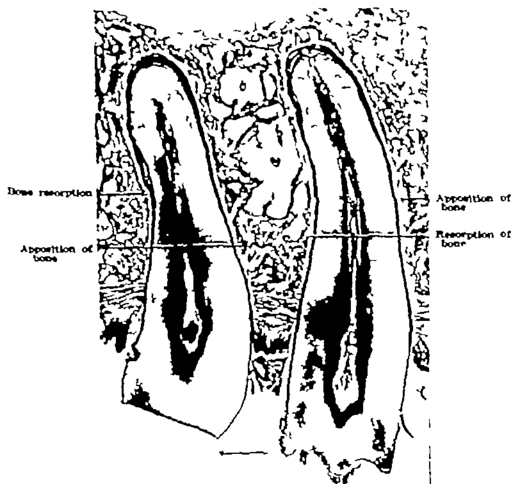


Fig. 74.—Mesial drift. Mesiodistal section through upper first and second bicuspids. Arrow indicates direction of movement. Apposition of bone at the distal surfaces, resorption of bone on the mesial surfaces of the alveoli. (Weinmann.)

is, like osteoid tissue (the uncalcified bone), highly resistant to resorption. By its continual growth the root protects itself against resorption under normal conditions.

Alveolar bone grows throughout life. This growth, however, is restricted to certain small areas of the alveolar surface. Apposition occurs, normally, at the alveolar fundus and at the distal wall of the alveolus (Fig. 74). Apposition of bone in these areas exerts a slight pressure on the tooth. The cementum on the root does not react to this pressure by being resorbed since it is protected

Bone resorption

Bone apposition

A *B*

Fig. 75.—Details from the alveolar wall of the second bicuspid shown in Fig. 74 (Original magnification ×120 reduced to ⅘.)

A. Mesial periodontal membrane. Resorption of the alveolar bone.

B. Distal periodontal membrane. Apposition of bone at the alveolar wall.

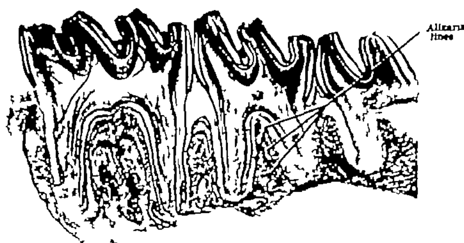


Fig. 76.—Sagittal ground section through mandibular molars of a rat which had received three alizarin S injections. Bone apposition at the alveolar crests and at the distal surfaces of the alveolar septa. (Original magnification ×20 reduced to ¾.) (Sicher and Weinmann.)

its own growth potential Therefore, the slight pressure exerted by the wth of bone opposite the apex and distal surface of the tooth leads to a ement of the tooth occlusally and mesially The mesial movement of the h in turn exerts a slight pressure directed toward the bone of the mesial l of the alveolus, and as a result of this pressure resorption of bone occurs his area (Fig 75)

The resorption on the mesial alveolar wall in man or more generally on alveolar wall toward which the teeth move is not a continual process (Figs. nd 77) It occurs in waves, each of which is followed by a period of repair s is in accordance with a rather general rule that resorption of bone in wth and under pressure overshoots its mark so much bone being removed t reconstruction by apposition of bone can follow immediately During rement of teeth this period of repair is of special importance because it mits the reattachment of suspensory fibers of the periodontal membrane

Occlusal movement of the teeth during the functional period of eruption is, ing the years of growth, correlated with the vertical growth of the maxillary l the mandibular alveolar processes which occurs at the free borders of the eolar bone The occlusal movement also compensates for the attrition of teeth at their occlusal surfaces.

Mesial movement of the teeth may be considered as an adaptation to the tinual loss of tooth substance at the contact points. The teeth are kept in e contact by the mesial drift despite the wear at the contact areas.

Growth of the Pneumatic Cavities of the Skull.—Development and wth of the air filled cavities of the skull can be understood only if their func al significance is clarified. These spaces develop as invaginations of the al cavity or the cavity of the middle ear into the adjacent bones. They nain in communication with the cavity from which they originate and are ed by an extension of the mucous membrane of the respective cavity

These spaces can be likened, in a mechanical way to the large marrow ces in the long bones. The marrow space replaces the central part of the ft of a long bone where bony substance would not contribute materially a greater mechanical efficiency of the bone A solid bone would carry only lightly greater load, but would be heavier and would need stronger muscles its movement and thus the level of functional adaptation would be lowered. chanical requirements of the same type are at work in certain regions of the ill. Wherever the spongy core of a bone of the skull is not under mechani l stress, the bone tissue is removed. However marrow is not deposited in its ace rather the bone is made hollow by a diverticulum of the adjacent air nducting passages. This explains the peculiarities in the development and owth of the air spaces of the skull and eliminates many erroneous interpretions. It is, for instance, contrary to the sequence of events to contend that bone failed to grow to its normal size because the air space contained in it d not fully expand. In reality just the reverse is true. The growth of the

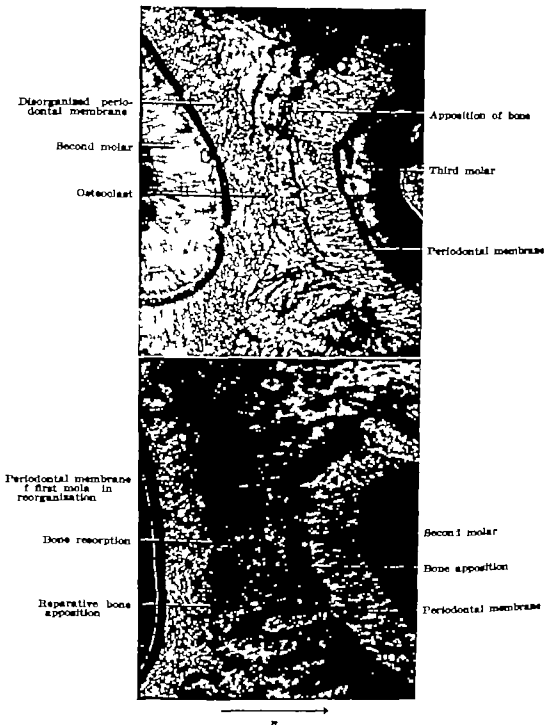


Fig 77 —Alveola septa from horizontal sections through the mola region of rats. The molars mo e distally i th d rection of the arrow Alternating resorption and repai of the al eolus and concomita t disorganization and reorganization of the functional structure of the periodontal membran (Sicher and Weinmann)

A. Septum between mand bular secon l and third molars. Resorption opposite the second mol is at its h ight disorganization of th corresponding part of the periodontal membrane.

B Septum between mandibular first and second mol rs. Islands f reparative apposition on the resorbed bon surface pposite the first mol ; beginning reorganization of the periodontal membrane i this area.

bone was inhibited primarily and therefore the air space hollowing it out remained smaller than normal. It is also a confusion of cause and effect to maintain that bones enlarge because the included air spaces expand. The overgrowth of the bone is primary, the expansion of the sinus secondary.

From this point of view it can also be understood that air sinuses enlarge at an age when normal growth of the body has ceased. The enlargement of certain sinuses in old age is explained by the fact that at this time the mechanical stresses in the skull diminish, especially if the teeth are lost and the masticatory apparatus is weakened. It can also be understood that certain sinuses extend sometimes in a rather irregular manner if parts of the bone which they occupy lose their functional significance (Fig. 78).

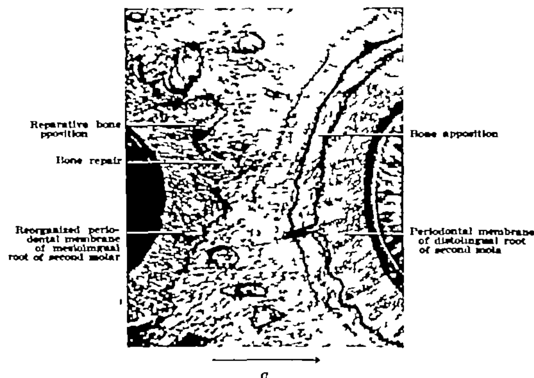


Fig. 77 (Cont'd.)—C. Septum between the lingual roots of maxillary second molar. Progressed reparative apposition opposite the mesiolingual root; complete reorganization of the periodontal membrane in this area.

The air spaces which have to be considered in this chapter are the following: frontal sinus, maxillary sinus, and sphenoid sinus, all evaginations of the nasal cavity, and the cells of the mastoid process originating from the cavity of the middle ear.

The frontal sinus develops at the time when the supraorbital ridge arises as a buttress for the masticatory forces. In the first year of life the outer and inner plates of the frontal bone are closely applied to each other, whereas later the outer plate is "folded away" from the inner plate and a potential space is created between the two compact layers of the bone. Into this space

extends a diverticulum of the most anterior cell of the ethmoidal labyrinth and this cell thereby gives rise to the frontal sinus. The enlargement of the sinus proceeds simultaneously with the differentiation of the supraorbital region and is directed upward and laterally. The two sinuses, which are nearly always *asymmetrical, are separated from each other by a thin irregularly bent* septum. In later years, when loss of function or reduction of function of the masticatory apparatus permits a further thinning of the compact plates of the frontal bone, the sinus extends more and more and may then hollow out the orbital roof to a variable extent. This senile enlargement of the sinus furnishes additional evidence of the mechanical nature of the origin and growth of the air spaces. A thinning of the bones of the skull is a general feature of old age. Flat and wide depressions on the outer surface of the parietal bone,



Fig. 78.—Roentgenogram of the upper jaw. Maxillary sinus extends toward alveolar crest after loss of first molar. (From Orban: Oral Histology and Embryology.)

for instance, can often be observed in the skulls of old persons. Here the decrease in substance is effected by resorption of the outer surface of the bone. In areas where air spaces are contained in the bone, however, the bony plates are thinned out from within.

The sphenoid sinus of the adult is, in reality, the result of fusion of the posterosuperior recess of the nasal cavity with the cavity occupying the body *of the sphenoid bone. In the newborn infant the sphenoid bone* proper is solid; that is, it consists of uniformly arranged spongy bone. The sphenoid sinus is restricted to a small cavity surrounded by a thin bony plate, the sphenoid concha, which later fuses with the anterior surface of the body of the sphenoid bone. Only then, in the second year of postnatal life, the hollowing out of the sphenoid bone commences and thereby the development of the sphenoid sinus in the strict sense. The enlargement of the sinus proceeds into old age in many persons. In middle age the sinuses occupy the central part

of the sphenoid body separated from each other by a thin rarely symmetrical septum. They reach posteriorly to the level of the hypophyseal fossa which bulges into the cavity of the sinus at its superoposterior wall. Later the sinus may expand considerably in all directions. It may invade the occipital bone and the roots of the lesser wings and the pterygoid processes of the sphenoid bone itself If the expansion hollows out the root of the lesser wing the sinus envelops the optic canal more and more sometimes even surrounding it entirely with the exception of a thin plate of bone connecting the bony wall of the optic canal with the cerebral surface of the lesser wing A similar relation can develop between an inferior or pterygoid recess of the sphenoid sinus and the pterygoid canal The close relations of the sinus and the nerves contained in the optic or pterygoid canals may be of practical importance by involving the nerve in infections of the sinus.

The maxillary sinus develops as an evagination from the middle nasal meatus in the last month of fetal life At birth the sinus is still an insignificant cavity smaller than a pea (Fig 79) Its growth is largely dependent upon the eruption of, first the deciduous and then the permanent teeth. The germs of the deciduous teeth and later though to a lesser degree those of the permanent teeth are placed in the maxillary body Only after eruption of these teeth can the maxillary sinus expand and hollow out the space formerly occupied by the developing teeth. At puberty the maxillary sinus reaches its average size. At this time the sinus is bounded by thin bony walls toward the orbit, toward the canine fossa, and in the region of the maxillary tuber Downward it reaches into the root of the alveolar process.

The sinus continues to expand throughout life in most individuals. Most frequently it penetrates deeper into the alveolar process, thus establishing a more and more intimate relation to the apices of the roots of the second bicuspid and the three molars. In later age the sinus expands mainly in two directions. The zygomatic process of the maxilla is sometimes hollowed out completely and, after fusion of the zygomaticomaxillary suture, the sinus may even invade the body of the zygomatic bone Another expansion of the sinus is directed anterosuperiorly as the infraorbital recess. If it develops the infraorbital canal is increasingly carved out from the roof of the maxillary sinus. In fact, the canal may protrude almost entirely into the sinus, separated from its space by a thin plate of bone only even defects of this separating bony plate may develop Sometimes the maxillary sinus extends into the root of the palatine process, forming the palatine recess, and sometimes it extends into the postero-supero-medial corner of the maxilla and even into the orbital process of the palatine bone The gradual expansion of the maxillary sinus and the thinning of its anterolateral and posterolateral walls open, in most cases, the narrow canals of the superior alveolar nerves from within so that the nerves themselves for some distance are in immediate contact with the lining membrane of the sinus. This is the reason why an acute inflammation of the sinus is frequently accompanied by pain in groups of maxillary teeth.

The pneumatic cells of the mastoid process develop simultaneously with the mastoid process itself. At birth the mastoid process is absent, and of the pneumatic cavities, only the mastoid antrum, a posterosuperior recess of the middle ear cavity is established. This is the point from which the gradual pneumatization of the mastoid process commences in the second year of life.

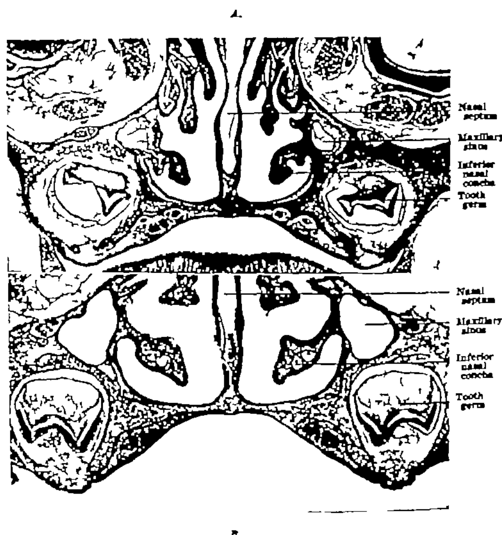


Fig. 79—Frontal sections through the head. (From Orban Oral Histology and Embryology.)
A Newborn infant.
B Nine-month-old child.
Compare the size of maxillary sinus.

We do not have an explanation for the fact that the mastoid process is not hollowed out by one air cavity but by a system of communicating cells. The size and number of these cells are variable and occasionally their development is entirely suppressed. In such instances the mastoid process is filled with a more or less dense spongiosa.

FUNCTIONAL ADAPTATION OF BONES

Introduction.—The interdependence of structure and function is one of the fundamental laws of biology. The shape and structure of bones with their pre-eminently mechanical function can serve as a good example for the validity of this law. Here a mathematical analysis of the forces acting upon a bone is possible and the results of this analysis can be compared with the actual structure of the skeletal element. The findings can be summarized in the following statement: the outer form and the inner structure of a bone enable it to resist the maximum force with a minimum of material.

Although the structure of a bone, under both normal and pathologic conditions, is dependent upon its function, the latter does not play any role in the first stages of the development of a bone. Experiments have shown that chorio-allantoic grafts from the basal half of the posterior or anterior limb bud of a chick embryo develop to a fairly normal femur or humerus. It can be assumed that this phase of self-differentiation does not last very long. Soon some extrinsic factors, such as pressure of adjacent organs, gain increasing influence upon the modeling of the developing bone. The final shaping of a skeletal element and the final elaboration of its internal structure occur only under the influence of normal function. The human calcaneus, for example, attains its normal shape and structure only in individuals who develop normal posture and gait.

Not only does shape and structure of each bone conform to a "law of economy," the arrangement of muscles, tendons and ligaments also increases greatly the mechanical efficiency of the skeleton, while it reduces at the same time the amount of bone tissue. The most dangerous force acting upon a bone (or most any other material) is a bending force. By arranging muscles and their tendons so that they counteract bending forces exerted, for instance, by the body weight, carrying ability of the bones is greatly increased. An example is that part of the gluteus maximus muscle that continues as the iliotibial tract of the fascia lata to the tibia. Tensed by the contraction of the gluteus maximus and tensor fasciae latae muscles, this tract exerts an outward bending force upon the femur at the same time when the load of the trunk tries to bend the femur inward.

Another example of a slightly different type of mechanical arrangement can be observed in the action of the masseter muscles. The masticatory forces attacking the upper facial skeleton via the maxillary teeth bend the zygomatic arch upward while the direct pulling force of the masseter tends to bend the zygomatic arch downward. The latter forces are also resisted by the suspensory action of the temporal fascia.

By studying models, made of plastics, in polarized light, the lines of stresses can be made visible. Studies on such models have shown that the muscles either attached to a bone or bridging it also reduce the bending force, in other words, increase the efficiency of the bone. Monarticular muscles reduce the bending forces in that part of the bone that lies between their attach

ment and the articulation that they move Diarticular muscles relieve bending stresses in the entire bone over which they pass. Broad attachment of muscles to bone flattens the spike of the bending forces otherwise concentrated in a small area.

Structural Analysis of the Femur.—In a long bone, for instance, in the femur the following structural peculiarities are of great importance (1) A compact cortical layer of bone of considerable thickness forms the tubular shaft of the bone. (2) The extremities of the bone the head, neck, trochanters, and condyles, consist almost entirely of cancellous bone with only a thin cortical layer of compact bone. (3) A large part of the shaft is occupied by the central marrow cavity only a few irregular trabeculae of spongy bone project

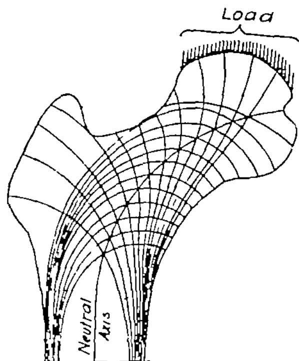
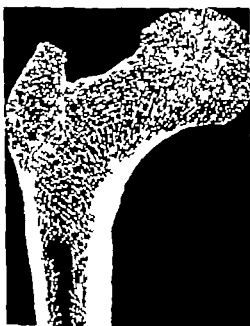


Fig 80—Diagram of the lines of stress in the upper femur (John C. Koch.)

from the compacta into the marrow cavity The spongy bone of the two extremities does not show an even distribution of trabeculae. Instead, the stronger trabeculae are arranged in orderly tracts, whereas thinner and shorter trabeculae connect the tracts with one another Such tracts of strengthened trabeculae in the spongy bone coinciding in all bones in every detail with the lines of stress, are designated as trajectories. The lines of stress are known as trajectories and the use of the same term for the systems of trabeculae following the lines of stress seems justified and convenient.

The most detailed studies of the mechanical structure of bones were made on the femur In normal upright position the load on the femur is about thirty per cent of the body weight and is impressed upon the upper surface of the femur head (Fig 80) This load is transmitted to the shaft by the long

obliquely planted neck and then down through the flaring distal extremity the condyles of the femur to the tibia The neck of the femur is subjected to compression and tension The lines of stress counteracting these forces curve gracefully from the upper and lower surfaces of head and neck into the upper end of the shaft where they enter the compacta of the shaft. The main trajectories of the proximal extremity of the femur follow exactly these lines of stress (Fig 81 1) One system of trajectories resisting the tensile forces originates, when viewed in a frontal section from the lateral surface of the shaft and curves upward and medially to end on the lower medial surface of the head and neck The compression trajectories arise from the medial surface of the shaft and fan out in an upward course to end on the upper lateral circumference of the trochanter neck and head.





A. *B*

Fig. 81.—*A.* Frontal longitudinal mid-section f upper femu The spongy bone is composed of two distinct systems of trabecula rranged in curved paths

B Frontal longitud nal mid-section of distal part f l ft femur Two main systems of trabeculae, a longitudinal and a transverse, can be seen. (John C Koch.)

These two main systems of trajectories crossing each other at right angles are arranged symmetrically around the neutral axis which starts on the fovea capitis and can be followed through the neck and into the shaft. It is note worthy that all these trajectories end at right angles on the cartilage-covered articular surfaces.

The reduction of the bone of the shaft to a hollow tube of compact bone is again an expression of the law of economy to achieve maximum strength with a minimum of material. Bending forces are best counteracted by material placed at some distance from the neutral axis. A given amount of material can resist bending forces much better if it is in the form of a hollow tube rather

than a solid rod. The bending forces are of course strongest in the middle of the shaft and diminish toward the two extremities The gradual reduction in the thickness of the compact bone of the shaft proximally and distally is in perfect correlation to these mechanical conditions.

Through the lower end of the femur the load is transmitted to the tibia in an almost straight line through a movable hinge joint. The mechanical conditions are fully answered by the flaring of the distal end to enlarge the contact areas and by the arrangement of the trajectories in vertical parallel tracts (Fig 81 *B*) These vertical tracts are buttressed against each other by short, thin, horizontal trabeculae. The vertical trajectories end at right angles to the condylar articular surfaces.

Experiments with a coating of a lacquer stress-coat that cracks under even slight deformation have shown that the danger areas in the femur are the areas subjected mainly to tensile forces. These are the upper surface of the neck and the lateral surface of the upper part of the shaft Generally it can be said that fractures occur most often in areas of tension.

Wherever the mechanical conditions of a bone have been investigated thoroughly the close correlation of structure and function has been fully established As an example, a comparison between the shaft of the femur and the body of a vertebra is highly instructive. The load upon a lower lumbar vertebra is greater than that upon the femur Still, a vertebra consists of spongy bone bounded by a mere semblance of a compact lamella. The reason for this is that the short body of a vertebra is almost entirely under pressure in a vertical direction only bending forces are almost completely absent. The bony substance in the shaft of the femur is condensed into the thick but hollow bony tube to resist the bending forces which here are inseparably linked with those of pressure

Functional Analysis of the Facial Skeleton.—In a study of the functional or mechanical adaptation of the skeleton, the bones of the face are of great interest, partly because of the striking differences between the upper and lower jaws and partly because of the presence of pneumatic cavities in the upper facial region

The mandible, movable against the skull has to be sufficiently strong in itself (Fig 82) It possesses a thick cortical layer of compact bone which is further strengthened along the lower border of the mandible The upper facial skeleton is anchored to the cranial base and is developed in certain areas into strong pillars consisting partly of thickened compact bone and partly of trajectories of the spongiosa. Between these pillars the bone remains thin and forms the walls of the various cavities.

The mandible resists bending forces with its strong compact layer The compact shell is filled with cancellous bone forming and surrounding the sockets of the teeth. The masticatory pressure exerted upon the teeth is transmitted as traction to the alveolar bone proper (lamina dura) via the principal fibers of the periodontal membrane The alveolar bone proper tends

to sink into the bone this tendency is counteracted by the spongy bone around the alveolar bone proper These trabeculae arise on the outer surface of the lamina dura and are arranged in an approximately cone-shaped field and end in part on the compact alveolar plates or on the laminae of adjacent teeth In contrast to the alveolar bone proper the spongy trabeculae and the compact alveolar plates are designated as supporting bone of the alveolar process.

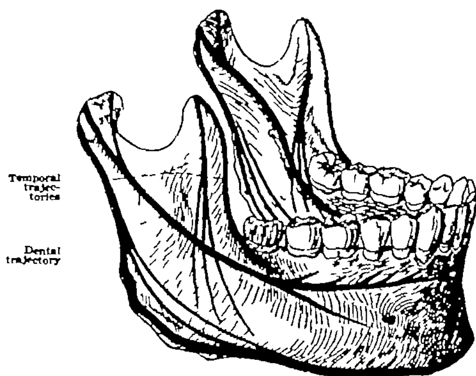
Some of the spongy trabeculae surrounding the apical part of the sockets unite as a trajectory which runs backward below the sockets and then diag onally upward and backward through the ramus to end in the condyle In this way the masticatory pressure is finally transmitted to the base of the skull. This most important trajectory of the mandible, the dental trajectory bulges on the inner surface of the ramus as a blunt crest the crest of the mandibu lar neck (Fig 82)

Other trajectories of the mandible are formed in response to the direct forces applied by the muscles of mastication. One is found in the region of the mandibular angle another starts at the tip of the coronoid process, fanning out into the mandibular body Between these trajectories there is one region of the mandible above and in front of the angle, where the cancellous bone is almost free of stresses. This is the region in which the trabeculae of the spongy bone are thin and the marrow spaces wide, a fact which can also be verified from observation of roentgenograms.

The region of the chin is especially endangered if bending forces act upon the mandibular body The bending force is exerted mainly by the medial component of force of the obliquely arranged external pterygoid muscles. If the two external pterygoids are forcefully contracted, the mandibular condyles are pulled medially and the mandible is measurably deformed. The mental region is therefore strengthened not only by the rather massive compacta of the mental protuberance, but also by trajectories of the spongiosa. These tracts of tra beculae cross each other at right angles, running from the right lower border of the chin upward to the left into the alveolar process and vice versa.

The upper jaw and the skeleton of the upper face form mechanically a unit anchored to the base of the skull. On each side three vertical pillars can be distinguished All of them arise in the basal part of the alveolar process and all of them end on the base of the skull. The three pillars are the canine pillar the zygomatic pillar and pterygoid pillar Their courses are not straight because they have to curve around the nasal cavity and orbit These curves of the pillars necessitate the presence of horizontal connections which act as buttresses (Fig. 83)

The canine pillar originates in the region of the socket of the upper canine and follows, first the lateral border of the piriform aperture, continues as the frontal process of the maxilla and ends on the medial edge of the supraorbital rim. In its inferior part it is interposed between the nasal cavity and the maxillary sinus. In this region it consists normally of a compact outer layer and a dense spongiosa in the center This part of the canine pillar is triangu lar in cross section.



A



B

Fig. 8. — The trajectories of the lower jaws. (Sicher and Tandler.)
A. Diag[illegible]
B. [illegible] through the ramus, showing the oblique direction of the spongy plates.

The zygomatic pillar originates in the region of the upper first molar as the zygomaticoalveolar crest which continues in a laterally concave course in to the zygomatic bone itself In its inferior part the zygomatic pillar consists of the strengthened compact lateral wall of the maxillary sinus it is V shaped in cross section. In the body of the zygomatic bone the lines of stresses divide. One tract is formed by the ascending frontosphenoidal process of the zygomatic bone abutting against the zygomatic process of the frontal bone which juts downward at the lateral end of the supraorbital rim The second division

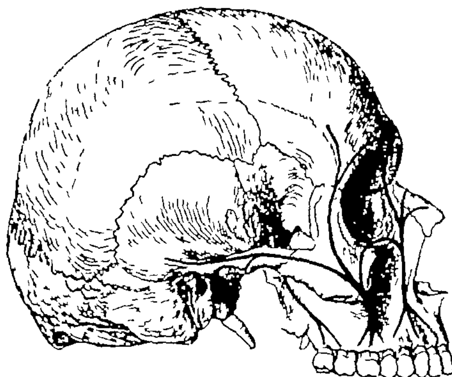


Fig. 41—The pillars of the skeleton of the upper face (diagram) (Sicher and Tandler)

of the zygomatic pillar is the zygomatic arch which is anchored at the base of the skull as the articular tubercle and as the horizontal root of the zygomatic arch or supramastoid crest

The pterygoid pillar is the pterygoid process of the sphenoid bone. Its lower end is joined to the posterior end of the maxillary alveolar process by the palatine bone Its upper end is anchored directly to the base of the skull.

The connections between the pillars are of great importance The canine and zygomatic pillars are connected below and above the entrance into the orbit by two crossbars of bone the infraorbital and supraorbital rims. The superior buttress seems to be especially important as a locus of resistance for the forces transmitted to it by the two anterior maxillary pillars There seems to be justification for the opinion that the extreme development of the supra

orbital region into a supraorbital torus is an adaptation to extremely high masticatory pressure and the strong prognathism. This is why the extinct and primitive races of man possessed a mighty supraorbital torus.

The connection between the upper ends of the horizontal zygomatic and the pterygoid pillars is a simple strengthening of the bone in front of the oval foramen connecting the articular tuberculum with the root of the pterygoid process. The system of pillars on one side is connected with that of the other side by the hard palate, forming a vaulted arch between the base of the right and the left alveolar process.

Between the pillars of the upper face and the nasal cavity on one side, and between the base of the alveolar process and the orbital floor on the other side, bony substance would be superfluous because it could not contribute to a further strengthening of the maxillary skeleton. Bone wherever it loses its mechanical function, is eliminated by resorption, and in this instance the spongy substance of the growing maxillary body is removed. The maxillary sinus, a diverticulum of the nasal cavity lined by mucous membrane and filled with air extends into the body of the maxilla.

Wolff's Law of Transformation.—If it be true that functional stresses shape the bone, then it is equally true that a change in the strength or direction of forces will lead to changes in the form and structure of bones. Generally it can be said that change of function in the young growing skeleton leads to changes of shape and structure in the older fully grown bones to changes in structure mainly It is as if the growing bone would grow into a new pattern determined by the new mechanical forces, while the fully grown bone has become more rigid in its outer shape but can adapt to changed forces by a new orientation of its structural elements. Examples of the validity of this statement often called Wolff's law are innumerable Lack of function leads to loss of bone tissue osteoporosis increased function may lead to the formation of more than the normal amount of bone osteosclerosis. This can be seen in kyphosis, wherein certain vertebrae are unevenly stressed (Fig 84) One side of a single vertebra may be under increased pressure the other may be almost relieved of any weight In the part of the vertebra which is under intensified pressure, the number of the spongy trabeculae is increased and each one is thicker than normal. As a consequence the bone marrow spaces are narrowed. Just the opposite is true of the relatively inactive part of the vertebra where the trabeculae are thinner and fewer and the marrow spaces wider than normal. Another typical example of osteoporosis caused by lack of function (disuse atrophy) is the reduction of the supporting bone around a tooth which has lost its antagonist (see page 196)

The great changes occurring in a bone after the healing of an incompletely reduced fracture are well known. It is clear that in such cases the united fragments are subjected to forces which differ in direction, if not in strength from the normal forces. In adaptation to these changes in functional stress, the bone is partly resorbed and rebuilt so that gross irregularities of its outer

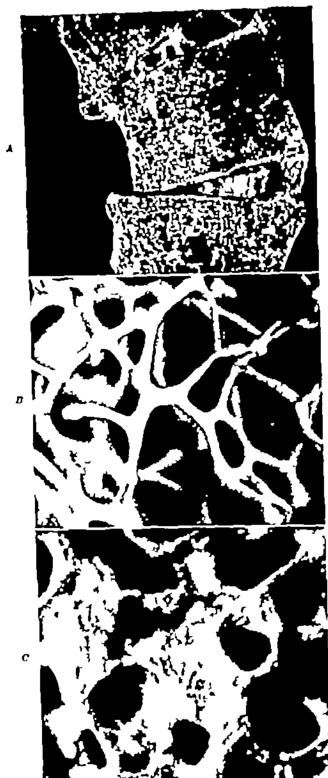


Fig. 84.—Changes in the structure of a vertebral body in scoliosis. (After W. Putschar.)
A. General view. Osteosclerosis on the concave side; osteoporosis on the convex side.
B. In the porotic area the thin trabeculae of the spongy bone are widely spaced.
C. In the sclerotic area the trabeculae are transformed into wide and thick plates, the marrow spaces reduced.

form are reduced and the direction of spongy trajectories is made to coincide with the new lines of pressure and tension Similar observations can be made in cases of ankylosis (see page 175)

Osteophytes.—Another pertinent example of functional adaptation can be observed in the formation of osteophytes. Osteophytes are bony outgrowths which arise as thin trabeculae from a bony surface and are generally at a right *angle to this surface. At some distance they are connected by crossbars of bone* which are arranged parallel to the old surface. Upon these crossbars a second and even a third tier of such regularly arranged spongy trabeculae may develop each generally consisting of thinner and shorter trabeculae than the preceding The osteophytes always consist of primitive, immature, coarse fibrillar bone.

Osteophytes are sometimes considered as the response to specific diseases of bone (tuberculosis syphilis) This opinion is erroneous. Osteophytes develop also on bones which are the site of an unspecific inflammation, of a tumor and sometimes during orthodontic treatment on the periosteal surface of the alveolar plate toward which the tooth is moved (see page 203)

The common denominator in all these cases is a thinning and therefore, weakening of a bony plate The response of the organism depends upon the speed of the process which leads to a weakening of the bone. If the process is slow surface apposition of lamellated mature bone will occur on the surface opposite that which the forces attack. If, however the process is rapid, the weakened bone is strengthened by what could be called an emergency measure. For this reason spongy bone of an immature character is built.

Osteophytes are therefore an unspecific and temporary emergency repair for bone which is weakened by any destructive process.

Reaction of Bone to Pressure and Tension.—It has not yet been successfully explained how mechanical forces stimulate the apposition of bone and how lack of function brings about bone resorption. The most probable hypothesis assumes that among others, mechanical, possibly vibratory stimuli cause formation of new bone They are therefore necessary for the replacement of bone that is lost in the normal course of events. Disuse atrophy is then not so much a direct loss of nonfunctional bone, but a lack of replacement of lost bone The experiments, made to elucidate these phenomena, have attempted to establish laws for the behavior of bone subjected to continuous or intermittent pressure or tension. The results of these experiments are very confusing and in many cases contradictory

Bone tissue as such is resistant to pressure as well as to tension. One could assume that, roughly speaking the resistance to tension is the property of the uncalcified fibrils the resistance to pressure the property of the calcified cementing substance of the tissue The resistance to pressure is obvious in the body of a lumbar vertebra carrying the weight of the greater part of the trunk plus that of head and neck and the upper extremities. It is also obvious that the femur carries in normal posture about 30 per cent of the body weight and that at the same time the tensile forces, inevitably linked with bending

pressure are equally well resisted. And still pressure of an arterial aneurysm or a growing tumor against the circumference of a vertebral body or against the shaft of the femur leads to rapid destruction of bone

These paradoxical observations and contradictory experimental evidence on the behavior of bone under pressure of different degree direction and duration—whether continuous or intermittent—find a rather simple explanation. As long as pressure does not interfere with the blood supply and drainage of the bone tissue it is resisted and if increased within the limits of tolerance will even lead to formation of new bone Wherever pressure diminishes or destroys the blood supply of bone tissue or interferes with its venous drainage the inevitable reaction is resorption of bone

The anatomic basis for these differences is also quite clear Under normal conditions, pressure is transmitted to bone tissue via avascular tissues. Pressure upon the avascular articular cartilages, the avascular intervertebral discs, or the avascular fibrous covering of the mandibular condyle and temporal articulating surfaces cannot have any influence on blood circulation. If however pressure is exerted against a surface of a bone that is covered by periosteum, the blood vessels in this tissue are compressed, and since they send and receive innumerable branches into and from, the adjacent bone this tissue is doomed to destruction It is interesting to visualize in this connection that the resorption of bone is a cellular activity the cells, osteoclasts, being derived from the compressed connective tissue It is, therefore clear that too great a pressure crushing and necrotizing the connective tissue adjacent to bone will give again a paradoxical reaction. Though bone under such pressure may necrotize to a variable depth its removal is retarded. Only from deeper reserves of cellular elements, Haversian canals, or marrow spaces can the mobilization of osteoclasts occur and the necrotic bone is finally removed by undermining or retrograde resorption

Whether intermittent pressure is tolerated or even beneficial or whether it too leads to loss of bone depends entirely on its effect on the blood circulation but it seems to be very difficult to assess this factor

The reactions of the denture bearing areas in upper and lower jaws are proof of the high complexity of the problem of reaction of bone to pressure It is well known that a great number of patients show little if any loss of bone in the jaws under well-constructed dentures. Even frequent reparative apposition has been observed in the areas of pressure Though the intermittent nature of the pressure and its reflectory control are factors to be kept in mind there is one more peculiarity of this bone to be *considered*. The alveolar bone receives its blood supply mainly from the interdental arteries that pass through canals in the interalveolar septa. Even after loss of the teeth these arteries do not entirely disappear Thus in contradistinction to other bones the blood vessels of the alveolar ridges in an edentulous mouth receive their blood vessels mainly from the inside of the bone and only in part from periosteal vessels. This protected localization of the nutrient vessels may contribute to the relative resistance of the alveolar ridges to pressure

Many areas of the skeleton show a specialized adaptation to tensile forces. These are ridges and tuberosities to which ligaments or tendons are attached and the inner surface of the dental alveoli. These areas are characterized by the inclusion of great numbers of strong collagenous fiber bundles, Sharpey's fibers.

That in such areas increased traction leads to formation of new bone is illustrated by the increased height and area of muscle attachment in individuals with heavy musculature. Many of the sexual differences of the skeleton reflect the stronger average musculature of the male. Experimentally the formation of new bone on the site of traction during orthodontic tooth movement is another evidence of the stimulating effect of increased tension. It is, however, clear that increase of tension beyond the limits of tolerance will lead to injury not only of the tendons or ligaments, but also to a resorption of the bone of attachment. Here also the damage to bone tissue is the consequence of disruption of its blood supply or drainage after rupture of blood vessels during a tear of the attached structures.

In this connection the mechanics of the periodontal membrane are of interest. Pressure exerted upon the tooth is, via principal fibers of the periodontal membrane, transmitted as tension to the bone. Those who deny the suspensory function of the periodontal membrane and ascribe to it a cushioning function and thereby assume that the alveolar bone is under pressure should think more of biology and less of mathematics.

The influence of increased pressure or tension on bone can be summarized as follows:

1. Increase of pressure or tension beyond the limits of tolerance leads to destruction of bone by resorption.

2. Within the limits of tolerance, an increase of the normal forces of pressure or tension leads to formation of new bone if the forces act upon surfaces adapted to resist pressure or tension. Areas of pressure are characterized by a covering of avascular tissue. Increased traction in an area adapted to traction will also lead to apposition of bone.

3. Wherever pressure, whether continuous or intermittent, interferes with the blood supply or blood drainage of bone tissue, osteoclastic resorption of bone results.

4. If the vascularized connective tissue is destroyed, bone resorption is delayed and the necrotic bone is finally removed by retrograde or undermining resorption.

PART II

PATHOLOGY OF BONE AND BONES

CHAPTER III

DEVELOPMENTAL DISTURBANCES OF THE SKELETON

Many developmental disturbances of the skeleton are congenital; others become manifest during life. A clear distinction has to be made between the terms congenital and hereditary or genetic. A congenital disease may be genetic or hereditary, but it may also be caused by intrauterine trauma. The term congenital, therefore, should be used only to denote that a symptom or a syndrome is present at birth. On the other hand, a hereditary disease may be manifest or latent at birth, as are many normal inherited characteristics. It should also be emphasized that a genetic disease is hereditary but not necessarily inherited. It may and it does originate in a new mutation, the signs of which cannot be detected in the ascendancy of the affected individual. However, from its appearance it will follow in the descendants the laws of

genetics. Only those genetic and hereditary disturbances of bone and bones will be discussed the pathogenesis and pathology of which is fairly well known. It will be stressed again that such disturbances either influence bone as tissue or bones as skeletal elements.

In contrast to primary disturbances of the skeletal elements, the bones show secondary deformities when the respective part of the embryonic body has suffered a disturbance before the bones in the region have developed An example of this category of bone disturbances is the defect of the premaxillary bone in cases of harelip

GENERALIZED DEVELOPMENTAL DISTURBANCES OF BONE TISSUE

Osteogenesis Imperfecta

Symptoms.—Osteogenesis imperfecta or osteopsathyrosis, is an hereditary fragility of bones caused by marked osteoporosis. The disease occurs either as osteogenesis imperfecta congenitalis or as osteogenesis imperfecta tarda The first most severe type develops in utero The second, less severe, may commence at any time during childhood or adolescence The congenital type is transmitted by a recessive the milder type by either a dominant or a recessive gene The fragility of the bones in all cases of osteogenesis imperfecta frequently leads to fractures, often caused by a slight injury or during normal function (Fig 85) Children with congenital osteogenesis imperfecta are sometimes stillborn or die soon after birth. They may survive and experience spontaneous healing In such cases, the fragility of the bones seems to disappear at puberty In later years, otosclerosis leading to deafness may develop

Osteogenesis imperfecta is nearly always linked with a peculiar developmental disturbance of the teeth, dentinogenesis imperfecta, the teeth showing an amberlike translucency or opalescence and a marked progressive narrowing of the pulp chambers and canals The abnormality is restricted to the mesodermal dentin the ectodermal enamel is sound

Some authors have expressed the opinion that the genetic dysfunction of the osteoblasts and odontoblasts is only a part of a more general disturbance of the supporting tissues. The slight changes in the cartilage and especially the presence of the blue sclerae in many cases of osteogenesis imperfecta support this view The latter phenomenon is explained by abnormal thinness and translucency of the sclera The dark brown choroid membrane appears blue when seen through the semitranslucent medium of the sclera.

The variable onset and prognosis of the disease and the presence or lack of other symptoms, have led to a differentiation of three types of hereditary osteoporosis. The congenital type is described as osteogenesis imperfecta letalis (Vrolik) Fragility of the bones without any other symptoms is referred to as osteopsathyrosis or osteogenesis imperfecta, type Lobstein. Finally a type is described in which the hereditary osteoporosis is linked with blue sclerae and otosclerosis.

Osteogenesis imperfecta results from a deficiency of the bone tissue in quantity and quality This, in turn, is the consequence of some genetic damage to the osteoblasts, which seem to be retarded in their function and differentiation forming too little bone and at a slow rate and continuing to produce primitive coarse fibrillar bone at a time when normally lamellated bone should develop The osteoclastic activity is not increased and may even be reduced.



Fig. 55.—Osteogenesis imperfecta. Radiograms of the upper extremities showing osteoporosis and multiple fractures. (Courtesy Dr Poncher)

Histopathology —The defects of the bone tissue lead to severe defects of the bones. The principal pathologic change seems to be the lack of a normal compact layer in the diaphyses of the long bones, in the mandible, and, to a

lesser degree, in other bones. In place of a compact corticalis, a thin layer of loosely arranged immature spongy bone is found (Figs. 86 87 and 88) Fragility of such bones, therefore is to be expected

The cortical layer of the bones is deficient in length and does not extend into the metaphyseal area. Here where the corticalis functions as a supporting splint, the first signs of a mechanical insufficiency of the bones can be seen

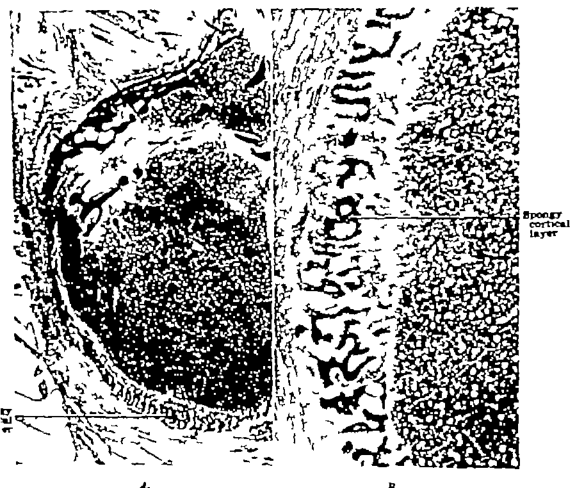


Fig. 86.—Osteogenesis imperfecta. Same case as shown in Fig. 85. Cross sections through the femur (Specimen, courtesy Dr Bennett)
A General view (Original magnification X1 reduced to [illegible])
B Detail (Original magnification X40 reduced to [illegible])
Note the absence of a compact cortical layer In its place primitive spongy bone is found.

in microfractures of the newly formed bone trabeculae and in numerous minute hemorrhages (Figs. 89 and 90) In such areas, the bone marrow is changed into a loose fibrous tissue

In spite of the lack of compact bone and the general deficiency of bone tissue there is some proof of functional arrangement of bone tissue and functional adaptation of bones that is, the increase in number of the delicate



A,

Fig. 87 —Cross section through the mandible in osteogenesis imperfecta, *A* compared with the mandible of a normal child of the same age (nine months) *B* (Magnification X9)

A Note the general reduction of size of the mandibular body, the thin spongy layer functioning as corticalis, and the large uniform marrow space. (Specimen, courtesy Dr Massler)

B Note the dense arrangement of the spongy bone in the interior of the mandibular body, dividing the marrow space into numerous small spaces. The cortical layer is strongly developed on the buccal side of the body

metaphyseal trabeculae and the arrangement of trabeculae in bones which are bent after a fracture. The overproduction of longitudinal and parallel trabeculae at the concavity can be understood only as an adaptive reaction (Fig 91)



D

Fig 87 —(For complete legend see opposite page)

Pathogenesis.—The growth of the long bones in thickness is more or less impaired. The growth in length is almost normal. This seeming contradiction is explained by the fact that transverse growth depends entirely on the activity of the osteoblasts whereas longitudinal growth of a long bone is primarily dependent on the growth of the epiphyseal and the articular cartilages.

The cartilaginous growth and the calcification of the cartilage, preparatory to its resorption and replacement by bone, are normal in cases of osteogenesis imperfecta (Fig 92) The fact that the residual spicules of cartilage are in completely covered by bone does not interfere with the elongation of the bones. The shortening of the limbs in cases of osteogenesis imperfecta is due to the multiple fractures. It is interesting that these fractures begin to heal very readily by formation of great masses of cartilaginous callus bony union, however is considerably retarded



A B.

Fig. 93.—Details of the sections shown in Fig 87 (Original magnification ×110 reduced to ⅔)

A Th spongy cortical layer in osteogenesi imperfecta, consisting mostly of primitiv bone (Specimen, courtesy Dr Massler)

B The compact cortical layer of the mandibl of a normal hild consists almost entirely of lamellated bone

In the bones of the skull, there is the same evidence of diminished osteoblastic activity The bones of the base of the skull for instance, the petrous part of the temporal bone, especially the labyrinthine capsule, often contain abnormally large remnants of cartilage. The anteroposterior growth of the base of the skull being dependent on cartilaginous growth in the intersphenoid and spheno-occipital synchondroses, is not affected. The flat bones of the cranial vault are extremely thin and are sometimes represented by numerous isolated bony plates embedded in the otherwise membranous brain capsule.

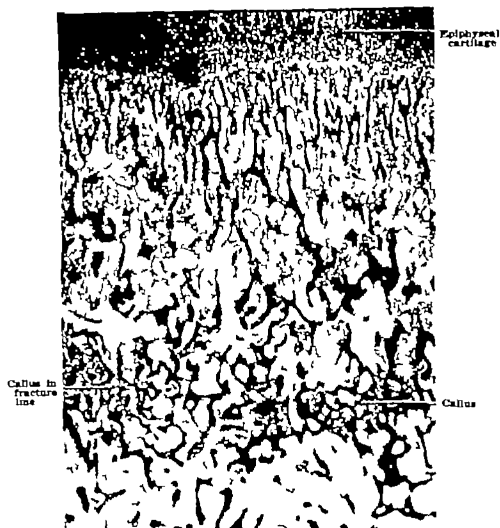


Fig. 83.—Distal metaphysis of the femur in osteogenesis imperfecta. Note the relatively dense arrangement of bone trabeculae and the formation of a callus at the line of metaphyseal infraction. (Original magnification ×40; reduced to [illegible].) (Specimen, courtesy Dr Bennett.)



Fig. 90.—Detail of the metaphyseal fracture shown in Fig. 89. N to the microfracture of the slender bone trabecul and the adjacent hemorrhages. (Original magnification X250 reduced to [illegible].) (Specimen, courtesy Dr. Bennett.)



Fig. 91.—Longitudinal section through the tibia in osteogenesis imperfecta. The curvature is the consequence of a fracture. Note the reinforcement by concentric trabeculae at the concavity. (Original magnification ×8, reduced to ¾.) (Specimen, courtesy Dr Bennett.)

All attempts to alter the course of the disease by dietary or hormonal therapy proved a failure.



Fig. 92.—Detail of the metaphysis of the distal end of the femur i osteogenesis imperfecta. The columns of the epiphyseal cartilage are fairly normal. Th remnants of the intercolumnar ground substance are covered by delicat layers f bone. (Original magnification ×250 reduced to ¾.) (Specimen, courtesy Dr Bennett.)

Osteopetrosis (Marble Bone Disease, Albers-Schönberg Disease)

Symptoms.—The hereditary generalized osteosclerosis, described as osteopetrosis, or marble bone disease, is, in some respects, a counterpart of hereditary generalized osteoporosis, or osteogenesis imperfecta.

Osteopetrosis is usually congenital but may develop early in postnatal life. The earlier the manifestation, the more severe the condition. The clinical symptoms are fragility of the bones severe osteosclerosis of all the bones club-like thickening of the proximal and distal ends of the long bones (Fig 93) the presence of alternating bands of more and less dense bone parallel to the epiphyseal plates narrowing of the optic foramen and internal acoustic meatus, possibly leading to a progressive disturbance of the visual and the acoustic

sense and loss of hemopoietic marrow possibly leading to anemia partly compensated by ectopic myelopoiesis in the liver spleen and lymph nodes. Anemia is sometimes absent in older persons In many cases, necrosis of the jawbones was observed as a consequence of odontogenic infection Cases have been reported in which tooth extraction led to fracture of the jawbone Callus formation after fracture approaches the normal.

Pathogenesis.—In spite of some discrepancies in the literature, it can be said that the primary cause of progressive osteosclerosis is a reduction in osteoclastic activity The clublike thickening of the metaphyses of long bones, for instance, is not due to an increased bone production but to a lack of modeling resorption The narrowing of the marrow cavity is not a consequence of intensified endosteal bone production but of failure of bone resorption which normally increases the diameter of the marrow cavity The reduction of osteoclasis is not primary The cells of the connective tissue have not lost the capacity of differentiating into osteoclasts, and the bone in marble bone disease is resorbable.

The lack of resorption seems rather to be the consequence of failure in timing of bone apposition and resorption. The apposition of bone is accelerated or its resorption retarded. This disharmony leads to a vicious circle especially during development and growth of the endochondral bones. The growth, the degeneration the calcification, and, finally the initial resorption of the epiphyseal cartilage are undisturbed. The apposition of bone upon the surfaces of the intercolumnar spicules of calcified cartilage proceeds until many of the spaces between the cartilaginous remnants are completely filled (Figs. 94, 95 and 96) That the apposition of bone occurs at a normal rate and that resorption which normally removes many of the newly formed trabeculae, is retarded seem probable from the observation of pronounced resting lines between the shell like layers of bone in the spaces between the cartilage spicules. Retarded resorption soon leads to the development of solid blocks of tissue consisting of a mosaic of calcified cartilage and primitive immature bone

The consequences of the formation of the sclerotic areas are twofold Resorption is rendered difficult and nutrition is reduced. Both conditions are caused by the elimination of the loose vascular connective tissue which normally fills the numerous and relatively wide spaces between the primary spongy trabeculae of the metaphysis. Thus, the wide area of contact between the newly formed bone and connective tissue is sharply restricted. Wherever connective tissue remains in contact with the bone a feeble attempt of the *osteoclasts* to remove the overgrown masses of calcified tissue is evident *Most of the osteocytes* have disappeared from the sclerotic areas, and the sclerotic bone must be regarded as necrotic (Figs. 97 and 98)

In spite of a considerable increase in mass, the sclerotic bone is mechanically inadequate There is, of course no functional arrangement of the bone since this is possible only through an alternation of resorption and apposition. Moreover the sclerotic bone consists not only of bone but also of an irregular mosaic of calcified cartilage and bone. Finally the mechanical resistance of

the bone tissue is further reduced by the necrosis of large areas of bone. The fragility of bone in marble bone disease is therefore the consequence of its structure and not, as some authors believe, of its chemical constitution.

The mechanical insufficiency of the bones leads to an attempt of the organism to strengthen the bones by the development of periosteal osteophytes,



Fig. 93A.—Marble bone disease. Pelvis and femurs of a fi e-yea -old boy. Note the clubbing of the ends of the long bone and the increased density nd th alternating li es of greater and lesser density parallel to the epiphyses. (Afte W. H. Clifton, A. Frank, and S. Freeman.)

which may reach a considerable volume around the shafts of long bones (Fig 99). The osteophytes are formed of spongy bone arranged in concentric shells around the sclerotic shaft. The picture resembles, in its essentials, that observed in fluorosis (see pages 300 to 308) and in syphilitic periostitis (see pages 352 to 354).

In the spongy bone of the osteophytic layers, apposition and resorption of bone can be readily observed (Figs. 100 and 101) seeming to confirm the interpretation of the sclerosis as caused partly by the peculiar spatial conditions of the metaphysis, where even slight retardation of resorption may have grave consequences. It is of considerable interest that the connective tissue in the spaces between the osteophytic trabeculae may differentiate into hemopoietic bone marrow and thus aid to compensate for the loss of blood forming tissue in the marrow cavity



Fig. 93B.—Marble bone disease. Note the marked involvement of the bones at the base of the skull as contrasted with those of the vault. The characteristic clubbing of the posterior clinoid process is seen. (After W. H. Clifton, A. Frank, and S. Freeman.)

The pathologic changes of the cranium also seem in accord with this viewpoint. The sclerosis is here mostly confined to the cranial base which develops as cartilage bone (Fig 93B). Osteophytic bone formation can be observed on the outer or inner surface of the bones of the calvarium and even in some of their marrow spaces (Figs. 102 and 103) although these bones seem normal otherwise. These peculiar findings can be explained by the mechanical conditions of the cranium, which has to be viewed as a functional unit, indeed as *one* bone. The mechanical insufficiency of the base of the skull leads to a mechanical insufficiency of the whole cranium, and the osteophytic reinforcement *on the* vault is the result. Secondarily the formation of osteophytes may lead to an osteosclerosis of the bones of the skull which are not primarily affected.



Fig. 94.—Marble bone disease. Endochondral growth zone of a vertebra. Note the solid masses of bone filling the spaces between the remnants of the cartilage. (Original magnification ×210 reduced to ⅗.) (Specimen, courtesy Dr Bennett.)



Fig 91.—Marble bone disease. Vertebra. Central sclerotic mass consisting of calcified cartilage and partly necrotic bone. Note the mosaic structure and the lack of connective tissue and blood vessels in this area. (Original magnification ×210 reduced to ¾.) (Specimen, courtesy Dr Bennett.)



Fig. 96—Marble bone disease. From a cross section through the metaphysis of a femur Note the large areas of solid calcified tissue. The layers of bone filling the spaces between the cartilage remnants are separated from each other by darkly stained resting lines. Osteoclasts in the loose connective tissue. (Original magnification ×210 reduced to ¾) (Specimen, courtesy Dr Bennett)

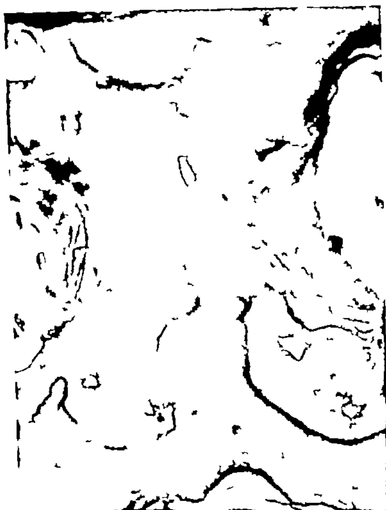


Fig. 97.—Marble bone disease. Detail of cross section shown in Fig. 96. Necrotic bone in the sclerotic area. (Original magnification ×980; reduced to %.)

The characteristic bands which can be seen in the roentgenogram in the otherwise homogeneous long bones can be explained as a sign of periodical remission of the disease (Fig 93*A*) It is probable that a slight increase in osteoclastic activity during a remission will find its expression mostly in the zone of epiphyseal growth. Here in an area of heightened cellular activity an increased resorption would lead to a more intensive resorption of the newly formed bone and calcified cartilage. Therefore, the trabecular network of



Fig. 9[illegible].—Marble bone disease. Detail of cross section shown in Fig. [illegible]. Necrotic bone is the sclerotic area. (Original magnification X250 reduced to ⅔)

bone formed during the period of remission would be primarily wider and would remain visible as a zone of a lesser density for a long period of time. Even a replacement of immature by mature bone may take place.

The disease is hereditary and seems to be transmitted as a simple recessive Mendelian character It is for this reason that osteopetrosis is often observed in the offspring of persons related by blood. Observations of the occurrence of the disease in members of two consecutive generations seem to indicate that marble bone disease or a distinct type of this disease may appear as

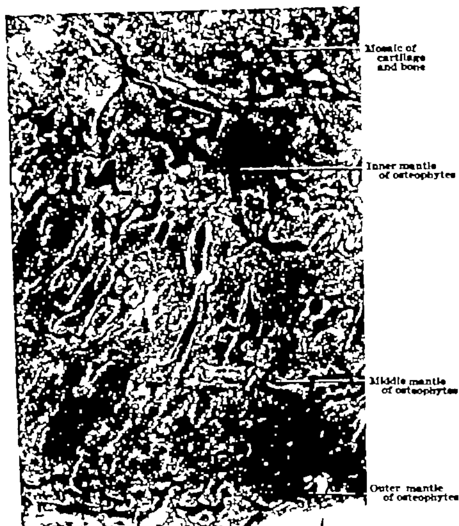


Fig. [illegible].—Marble bone disease. Cross section through the shaft of the femur. Note the osteophytic mantle around the sclerosed shaft arranged in tiers. The spaces between the trabeculae are filled with hemopoietic marrow. (Original magnification X3, reduced to ¾.) (Specimen, courtesy Dr. Bennett.)



Fig 100—Marble bone disease. Detail of cross section shown in Fig 99. The osteophytes consist of immature bone. (Original magnification X210 reduced [illegible] %)



Fig. 101.—Marble bone disease. Detail of cross section shown in Fig. 99. Apposition and resorption in the osteophytic bone. (Original magnification X210; reduced to 3/4.)

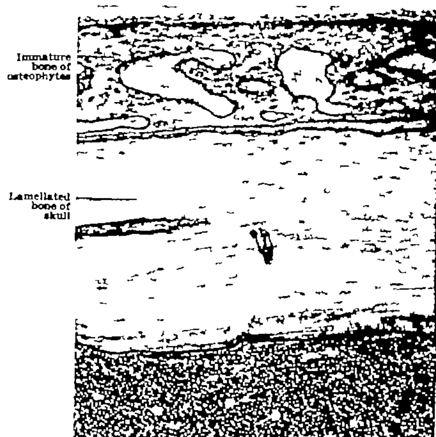


Fig 102.—Marble bone disease. Skull. Osteophytes, consisting of immature bone, on the surface of the outer plate which consists of lamellated bone. (Original magnification ×130 reduced to ⅔.) (Specimen, courtesy Dr Bennett.)



Fig 103.—Marble bone disease. Skull. Osteophytes in the diploic spaces which are filled with fibrous marrow. (Original magnification ×130 reduced to ⅔.) (Specimen, Courtesy Dr Bennett.)

a dominant mutation Investigations of the calcium phosphorus metabolism have led to contradictory conclusions. It is therefore impossible to decide the question as to whether a primary disturbance of the mineral metabolism is characteristic of osteopetrosis.

The Gray Lethal Mouse and the Incisor Absent Rat*

A mutation in the mouse characterized by the slate-gray color of its fur and by the severely restricted viability therefore gray lethal *gl* and a mutation in the rat, characterized by the failure of the incisors to erupt and, therefore, called incisorless, incisor-absent *ia* have in common a severe restriction of the resorbability of bone tissue. Both mutations are unifactorial and recessive The similarity of the behavior of bone tissue in these mutations should not be taken as an indication or proof that one deals in both cases with an identical mutation of identical genes or that the underlying biochemical mechanism of the disease is the same in the *gl* mouse and the *ia* rat. Despite the possibility of a different causation genetically and biochemically the symptoms in skeleton and dentition are so similar in these two animals that they justify a joint discussion.

Symptoms.—The most prominent symptom in both the gray lethal mouse and the incisor-absent rat is the generalized severe osteosclerosis of the entire skeleton. In the *ia* rat, this picture is transitory and resolution starts in the eighth week of life Because of the early death of the gray lethal mice the question of a possible recovery cannot be answered.

In the jaws, both strains of animals show impaction and deformities of many teeth The incisors cannot erupt because the proliferating epithelium invades the marrow spaces of the maxilla or mandible and, as a consequence an ankylosis develops between tooth and bone However since the proliferative activity of the odontogenic epithelium is not depressed, a pseudodontoma develops at the basal end of the incisors. Also the molars are similarly affected though the aberration is not as severe in the molars which are characterized by slower and limited growth. Healing of the osteosclerosis by gradual resumption of normal bone resorption allows in the *ia* rat a late eruption of the second and third molars that are always less severely affected. The osteosclerosis is also quite marked in all the other bones of the skeleton. The absence of resorption leads to a persistence of bone tissue that in normal animals is resorbed soon after it has been formed. Thus the appositional pattern of bone is preserved and much has been learned from a study on the skeleton of the *ia* rats.

The longitudinal growth of endochondral bones is normal because proliferation, degeneration, calcification and resorption of epiphyseal and articular cartilages and their replacement by bone are not impaired.

Pathogenesis.—It has been mentioned that the skeletal changes in both the *gl* mouse and the *ia* rat are caused by primary lag of bone resorption. This

* Similar conditions have been observed in mutations of the rabbit and occu normally in the manatee.

defect is not caused by an inability of the connective tissue cells to differentiate into osteoclasts. Therefore it seems probable that the cause of the disturbance of bone resorption is some defect in one or more of the many enzyme systems necessary for the normal function of the osteoclasts and possibly an altered chemistry of the bone tissue

The latter alternative seems somewhat supported by the different behavior of degenerated cartilage and bone. Although the mechanism of the resorption of these tissues seems to be in principle, identical, calcified cartilage is destroyed at a normal rate, while bone resorption is severely retarded

Injections of parathyroid hormone into young ia rats leads to a resolution of the osteosclerosis in the entire skeleton and in the jaws to a fairly normal growth and eruption of the teeth.

GENERALIZED DEVELOPMENTAL DISTURBANCES OF THE BONES

Chondrodystrophia Fetalis (Achondroplasia)

Symptoms.—Fetal chondrodystrophy a hereditary dysfunction of the cartilage is transmitted as a simple dominant Mendelian factor and causes dwarfism of a specific type. It is interesting to note that the incidence of chondrodystrophy rises with increasing maternal age Chrondrodystrophic dwarfs are characterized by extreme shortness of the limbs, shortness of the cranial base, and, therefore, deep saddling of the nose and marked bulging of the forehead. The upper jaw is retruded, the mandible often prognathous. There is no involvement of the endocrines. These dwarfs are of normal intelligence and sexually well developed. Many of them die at birth or shortly afterward, but they may live to an old age. This type of dwarfism has been known since time immemorial. Many persons so afflicted lived as kings jesters. Many are seen today in side shows

Pathogenesis.—Anatomically chondrodystrophy is a failure of the epiphyseal articular and basocranial cartilages to proliferate by interstitial growth and thus to prepare for the longitudinal growth of long bones and the anteroposterior growth of the cranial base The main sites of growth in the cranial base are the intersphenoid, the spheno-occipital and the intraoccipital synchondroses. The cartilage between the presphenoid and basisphenoid normally disappears in the last months of intrauterine life or immediately after birth the intraoccipital synchondroses fuse in the first five or six years, whereas the cartilage between the sphenoid and the occipital bone remains a site of growth until the sixteenth to the eighteenth year of life. In these synchondroses, the growth of the base of the skull occurs in exactly the same manner as the growth of the long bones in the epiphyseal cartilage Premature cessation of the cartilaginous growth and consequently premature synostosis of the bones of the cranial base, causes a permanent cessation of the growth in this region and a retrusion of the upper face Since the brain in chondrodystrophy grows normally in volume but is forced to change its shape the bones of the cranial vault bulge considerably and the bulging forehead especially enhances the impression of a deeply sunk and flat upper face

Protrusion of the mandible has often been observed. To the best of our knowledge, no explanation has yet been given for this rather puzzling fact puzzling because longitudinal growth of the mandible occurs in the secondary condylar cartilage by endochondral bone formation. The explanation for this paradoxical behavior seems to lie in the fact that the secondary hyaline cartilage of the mandibular head is itself covered by a thick layer of dense connective tissue Thus, the condyloid cartilage normally grows not interstitially but appositionally whereas an epiphyseal cartilage grows, in the long axis of the bone by interstitial growth only Since in chondrodystrophy only the interstitial proliferation of cartilage is arrested and not its appositional



Fig 104 —Chondrodystrophy Femur of a five-month-old child. Proximal epiphysis. Note the irregular arrangement of the cartilage cells and the severe restriction of cartilaginous growth. (Original magnification ×230 reduced to ⅘) (Specimen, courtesy Dr Bennett.)

growth the epiphyseal cartilages cease to grow altogether The appositionally growing cartilage in the condyle of the mandible however can continue its growth. Certain breeds of dogs, for example the bulldog King Charles, and Pekinese, which are characterized by cranial chondrodystrophy also show the disharmony between the upper and lower face.

Histopathology—The histologic changes in the epiphyseal cartilage of the long bones have been studied extensively The cessation of interstitial proliferation can be directly ascertained. The cartilage cells are irregularly distributed, and the characteristic cell columns are missing (Fig 104) Degeneration of the chondrocytes and calcification and resorption of the ground substance and its replacement by bone proceed, although in an irregular fashion The epiphyseal cartilage sometimes shows localized irregular proliferation and

sometimes foci of degeneration. The connective tissue in the vascular channels may proliferate and form what has been called periosteal stripes. This proliferation of the connective tissue seems to be only one sign of dysfunction of the cartilage. Some authors wrongly have ascribed peculiar functions to these periosteal stripes On one side, ossification of such stripes has been viewed as a compensatory mechanism for diminished longitudinal growth. On

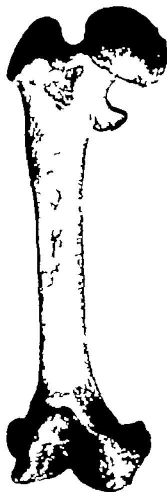


Fig. 105.—Femur of a chondrodystrophic female dwarf Note the mushroom shape of the head. (After Marum.)

the other side their development was seen as a cause for the curving of chondrodystrophic bones. Not one of these claims could be substantiated. Some epiphyses especially the heads of the femur and the *humerus*, show a peculiar mushroom shape in cases of chondrodystrophy (Fig 105) The wideness and flatness of these bony ends can be understood as consequence of the dual growth mechanism of the articular cartilage Its growth in thickness is entirely interstitial its growth in area is accomplished by appositional

growth at the borders, which are covered by an extension of the connective tissue of the articular capsule Arrest of interstitial growth of the articular cartilage will prevent lengthening of the epiphyses, which, however continue to expand at their periphery (see page 76) A similar mechanism leads to the formation of a rosary at the ends of the bony ribs, where they join the costal cartilage

The striking disharmony between the short extremities and the fairly normal trunk is, in all probability explained by the great number of centers of growth (intervertebral discs) contributing to the longitudinal growth of the vertebral column and by their stimulation by the growing viscera.

Formation and closure of the sutures and fontanels in the skull are normal except in cases of accompanying hydrocephalus. Development and eruption of teeth do not show any considerable disturbance.

The pelvis is significantly changed, a fact of great importance during pregnancy and parturition. Two types of pelvic deformities can be differentiated. In one type, the pelvis is flat anteroposteriorly The entrance into the pelvis is kidney-shaped, and the sacrum is almost horizontal. The second type shows a general narrowing without great deviation from the normal shape.

Chondrodystrophy in Animals.—Genetic disturbances identical or similar to chondrodystrophy in human beings have been observed in several animals. Best known are the bulldog calves in the Dexter breed of cattle and the creeper fowl More recently chondrodystrophy has been described in the rabbit and the guinea pig It has already been mentioned that the peculiarities of the skull in the bulldog and similar races and the peculiar shortening of the extremities in other breeds of dogs, for instance the dachshund are said to be restricted manifestations of chondrodystrophy It is interesting to know that in these animals the inhibition of cartilaginous growth is accompanied by other symptoms which vary in the different species. Despite this variability the animal material may still give valuable clues for an understanding of the disease in human beings.

Hereditary Multiple Exostoses

Symptoms.—One of the most frequent hereditary malformations of the skeleton is the development of multiple exostoses. Several terms are still in use for this pathologic entity the most appropriate of which seems to be the purely descriptive term of hereditary multiple exostoses. Because the exostoses consist partly of cartilage the term multiple cartilaginous exostoses was suggested. Since the malformation has its origin in some disorder of the growth of the skeletal cartilages, the term hereditary deforming chondrodysplasia is used by certain authors.

Although the disease is hereditary it is not manifest in the infant but develops gradually during childhood. The disease afflicts males as often as females. The genetic mechanism is not yet determined, and at the best it can be stated that the factor is dominant.

Clinically the hereditary multiple exostosis is characterized by the gradual development and growth of many knobby protuberances on different bones. The number of such exostoses can reach several hundred. The most frequent localization of the exostoses is the metaphyseal region of the bones at the knee, ankle and shoulder the scapula, the pelvic bone, the ribs, the vertebrae, and the bones of metacarpus and metatarsus. The bones of the skull are rarely involved. Symmetry of the excrescences is predominant unilateral development is rare. The growth of the exostoses is parallel to the skeletal growth, the exostoses ceasing to grow with the cessation of skeletal growth. If any one of the exostoses does grow after this period, the diagnosis of sarcomatous degeneration has to be considered.

In severe cases, the growth of the skeleton especially that of the long bones, is impaired, and the shortness of the limbs reminds one somewhat of the proportions in chondrodystrophy In addition, a peculiar curving of one or both bones in the forearm and the leg may occur which can lead to disarticulation of the forearm or hand and to severe restriction of movements.

The exostoses are restricted to the diaphyses of long bones and, in the ribs, mostly to their bony parts epiphyses of long bones are always free. This observation indicates that the exostoses develop in the growth zone of the cartilages close to the metaphyseal region of the bone and that they shift during growth to the diaphysis or in the ribs to their osseous part. The exostoses consist, at first, of cartilage which undergoes destruction and replacement by bone from its deep surface while the superficial layers continue to grow In later stages an exostosis consists of a base or a stalk and a core of spongy bone and a covering of hyaline cartilage. The marrow spaces of the exostosis communicate with those of the bone which carries the exostosis. Because of this peculiarity the exostosis cannot be regarded as a growth upon a bone but as a part of a disfigured bone. At the end of the normal growth period, the cartilaginous covering of an exostosis may disappear after total replacement by bone.

In other cases replacement of the cartilage of the exostosis by bone ceases soon after cessation of cartilaginous growth. Then a thin plate of bone is formed underlying the remnants of cartilage comparable to the terminal plate under articular cartilage.

The exostoses are covered by a layer of dense connective tissue, a continuation of the normal periosteum If a tendon slides over an exostosis, a synovial bursa may develop between the two

Pathogenesis.—A valid explanation of the mechanism by which the genetically determined exostoses develop has not yet been found. Most of the exostoses, if not all, develop from epiphyseal cartilage or from cartilage which serves an analogous function in the growth of bones. To assume that the multiple exostoses are caused by an abnormal manifestation of the dormant potency of the periosteum to produce cartilage is therefore improbable. It has been said that the abnormal proliferation of the juxtametaphyseal cartilage is

caused by the lack of a bony covering which normally is provided by the extension of the periosteal bony cuff of the diaphysis over the cartilage. Although the perichondral or periosteal bony cuff or collar often does extend beyond the plane of the metaphysis at the periphery of the cartilage such an extension just as often does not exist. Especially in the older stages of development of bones, the juxtametaphyseal cartilage is more often covered by perichondrium than by bone.

Since the multiple exostoses have to be considered as distortions of the normal pattern of a bone of which they form but a part, it seems reasonable to see the mechanism of their development in a distortion of the normal growth pattern of a bone. More specifically it is a distortion or a disharmony in the pattern of growth of the cartilage the proliferation of which achieves not only the enlargement, but also the primary molding of the bone. Growth of an epiphyseal cartilage is interstitial in the longitudinal and appositional in the transverse direction. The harmony between these two factors is necessary for the normal development. A break in this harmony and predominance of appositional growth must lead to the distortion of the bony outline by irregular lateral thickening. If the disturbance of the growth pattern of the cartilage is more severe there will be not only a plus in localized transverse growth, but also a minus in longitudinal growth. Because of the localization of the proliferative unbalance to a certain area of the circumference of the epiphyseal plate, the deficiency of longitudinal growth may also be restricted to a part of the cartilage while other parts continue a more or less normal proliferation. The consequence of such uneven longitudinal growth of the epiphyseal cartilage must be a curving of the involved bone. That in the forearm the ulna often is stunted in its growth while the radius is curved and relatively too long cannot be explained by the assumption that normally the growth increments at the distal epiphyses of the radius and ulna are different. It is well known that these bones grow at the wrist at an equal rate. The explanation seems rather to lie in the different transverse diameter of the radial and ulnar epiphyseal plates. A narrower plate will be more likely stunted in its longitudinal growth as a whole, while unequal growth can be expected in a relatively wide epiphyseal plate. The transverse diameters of the epiphyseal plate at the ulnar head are about one-third to two-fifths of those of the distal radial epiphyseal plate.

Cleidocranial Dysostosis

A familial and usually hereditary defect of the clavicles combined with defects of the cranial vault has been designated as cleidocranial dysostosis. Many authors saw in this pathologic entity a disturbance of the intramembranous bone formation. More exact studies have shown that this original concept is wrong. A clear picture of this interesting abnormality has not yet been formed. The findings, which vary from case to case can be summarized as follows: a unilateral or bilateral, total or partial defect of the clavicle leading to increased mobility of the shoulders, which, in extreme cases, can be brought to touch each other over the sternum (Fig. 106) retarded closure of

sutures and fontanels frequent development of numerous wormian bones retrusion of the maxilla and relative protrusion of the mandible possible underdevelopment of the lacrimal and zygomatic bones and occasional stunting of the long bones which are slender In contrast to these deficiencies in skeletal development, cases of overdevelopment of many or some of the long bones, for example second metacarpals and metatarsals, have been reported. Characteristic, also is the retarded eruption of the permanent teeth and the retention of the deciduous teeth sometimes to middle age. The roots of the permanent teeth are sometimes short and slender The frequent occurrence of supernumerary teeth is in striking contrast to the signs of dental defects enumerated here.

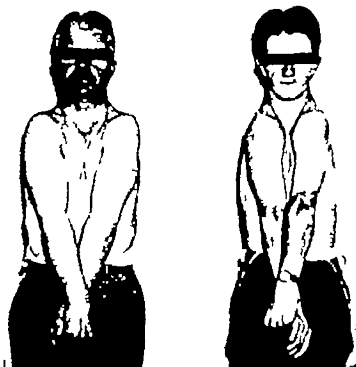


Fig. 104.—Cleidocranial dysostosis in a father and son. Mobility of shoulders is due to partial absence of clavicles. (After Decks.)

The preceding list of findings in cleidocranial dysostosis is proof that other than intramembranous bones are involved. The disease is, therefore, much more generalized than has been supposed. Whether we can speak of a disturbance of bone and dentin formation or of a disturbance of skeletal development is not yet clear since histologic investigation of this disease is lacking

Multiple Enchondromatosis

Multiple enchondromatosis, by some termed chondrodysplasia, is characterized by the presence of multiple enchondromas that are either congenital or develop early in life Although rarely more than one case in a family has

been observed, the disease is considered hereditary as a recessive mutation with very weak penetrance Males are more frequently affected than females. The extremities and the pelvis are most often diseased, less often the ribs and rarely the base of the skull. Sometimes the skeletal lesions are associated with multiple hemangiomas (Maffucci's syndrome)

Several types of the disease have been distinguished. Some of these types present apparently early and incomplete stages of the generalized form. Sometimes only one ray of an extremity for example, the radius and the thumb is affected in others only one arm or leg is diseased. It seems that acro-chondrodysplasia, affecting the metacarpal bones, metatarsal bones, and phalanges, and Ollier s disease in which one half of the skeleton is affected with a shortening of the extremities, represent disease entities, which can be distinguished from the complex and generalized type in which the entire skeleton is affected

In contradistinction to the multiple cartilaginous exostoses, multiple enchondromas are progressively growing during the entire life and frequently show sarcomatous degeneration. The tumors start to develop as enchondromas in the bone marrow cavity close to the epiphyseal plates, cause resorption of bone by their gradual increase in size grow through the compacta, appear *finally on the surfaces of bones, and lead to severe deformities. Foci of cal*cification in the multiple enchondromas or myxomatous degeneration are as frequent as in solitary chondromas.

Progressive Diaphyseal Dysplasia

The disease also known as Camurati Engelmann disease (hereditary multiple diaphyseal sclerosis) is characterized by symmetrical spindle-shaped thickening of the diaphyses of the long and short tubular bones. The marrow space is narrowed or obliterated In rare instances the *cranium mandible* vertebrae and pelvis are also affected The progressive bony *changes may lead* to disproportionate growth. The gait is impaired sometimes secondary muscular atrophy and pain are observed.

The histopathology has been studied on a *few biopsy specimens* only Our knowledge of the pathogenesis of the progressive diaphyseal *dysplasia* is as yet unsatisfactory

Generalized Osteochondrodystrophy

The common term of enchondral dysostosis or osteochondrodystrophy covers hereditary skeletal malformations of a bewildering variability The disease is caused by a symmetrical disturbance of cartilaginous growth often especially localized in the articular ends of bones. As a consequence of this distortion of the cartilaginous skeleton disturbances of the articulations are frequently observed, often leading to restriction but sometimes an increase of the mobility of the joints Curvatures of the bones may occur and also a severe change in the proportions of the body The changes in the vertebral column may lead to kyphotic or skoliotic changes. The skull also may be

involved to a variable degree In *severe cases a distinct type of dwarfism* may result, sometimes combined with peculiar facial deformities, often referred to as gargoyle face.

Several types of this disease have been differentiated, though there are transitional forms, which make the differential diagnosis difficult. The three types differ mainly in the severity of the symptoms, but also in their hereditary behavior The least severe type is the type Leri, which is inherited as a dominant mutation

The other two types show a recessive inheritance The type Morquio is less severe than the type Pfaundler Hurler The latter is, in addition, characterized by the presence of diffuse corneal opacity Of the latter type, an infantile and a late subtype are distinguished

Osteopoikilosis

Osteopoikilosis, also known as osteitis condensans disseminata spotted bones is characterized by the appearance of radiopaque areas in the epiphyses and metaphyses of the entire skeleton. The skull is only occasionally affected. *The disease is harmless without subjective symptoms, mostly observed in the* course of routine roentgenographic examination Most cases are solitary but familial occurrence has been observed. The disease is considered to be transmitted by a simple dominant gene. The radiopaque spots range in diameter from 1 to 5 mm. sometimes the radiopaque areas appear striated. Histologically the radiopaque areas consist of dense networks of delicate bone trabeculae

LOCALIZED DEVELOPMENTAL DISTURBANCES OF THE SKELETON

Primary Localized Disturbances

Primary localized disturbances of the skeleton seem to be rare There are many instances in which it is difficult to decide whether an anomaly of the skeleton is primary or secondary Examples of primary failure in development are the aplasia of the radius or ulna, the absence of the mandibular condyle, and the failure of the pelvic acetabulum to develop causing congenital dislocation of the hip

Secondary Localized Disturbances

Secondary developmental disturbances of the skeleton are more frequent If malformation of the embryonic body occurs before the skeleton itself develops, the skeleton is bound to adapt itself to the abnormal configuration of the part of the body in which it is placed. Lack of a part of an extremity or of the entire extremity will of course, be the cause of an aplasia of some or all the bones of the extremity In cases of polydactylism the supernumerary digit of the hand or foot develops in the bud stage of the extremity and may later develop its own skeleton Defects of the neural arches of the vertebra, spina bifida, are the consequence of primary disturbances in the development of the spinal cord

The importance of understanding these secondary skeletal malformations is best illustrated in the case of the cleft palate and the harelip

Cleft Palate and Harelip — 'The relation of harelip to the bone and to the teeth varies considerably In some cases the cleft corresponds to the suture between premaxilla and maxilla; in other cases, the cleft cuts through the premaxilla itself dividing it into a medial and a lateral part Frequently, the lateral incisor is found medially from the harelip in some cases laterally from it The lateral incisor is, in some instances, medially from the harelip and a supernumerary lateral incisor lies laterally from it. In other cases, the lateral incisor is missing The explanation for this variability is that the skeletal parts appear long after fusion of the facial processes has been completed. Thus, the bones develop in a uniform tissue and with no regard for the primary boundaries between the processes.

The dental lamina, the matrix of the tooth germs, is likewise independent of the facial processes. Harelip occurs in the general region of the lateral incisor In some cases, it may cut the matrix medially or laterally from the *prospective primordium of the lateral incisor* or it may go right through it In the latter cases, by a process of regeneration each part of the divided primordium may produce a complete lateral incisor or on the other hand the development of the lateral incisor may be suppressed altogether '[*]

Sicher H. Development of the Face and Oral Cavity in Orban, B. *Oral Histology and Embryology* St. Louis, 1944, The C. V Mosby Co.

CHAPTER IV

ADAPTATIONAL DEFORMITIES OF THE SKELETON

INTRODUCTION

PRIMARY CHANGES OF FORM

- Deformities of the Diseased Skeleton
- Deformities of the Normal Skeleton

PRIMARY CHANGES IN THE TOPOGRAPHIC RELATION OF BONES

- Immobilization by Ankylosis
- Imbalance of Mechanical Forces
  - Coxa Valga
  - Scoliosis
- Permanent Dislocation of Joints
- Pathologic Relaxation of Ligaments
  - Pes Planus (Flatfoot)

PRIMARY CHANGES OF MECHANICAL STRESSES

- Increase in Function
- Lack of Function
- Effect of External Forces
  - Cultural Customs
  - Habits
  - Therapeutic Appliances

INTRODUCTION

The law of transformation of bones as expressed by Wolff maintains that primary changes in form and function are followed by determinable changes in the outer shape and the inner architecture of the involved bone This law is based on the fact that each bone is, in shape and architecture, fully adapted to the mechanical forces which act upon it. Observations confirming Wolff's law of transformation are innumerable The following discussion is not intended to give a full account of all the clinical pictures which could be summarized under the heading of pathologic deformities of bones, but the working principles will be classified, studied, and illustrated by a few examples.

A deformation of one or more bones may occur in a normal or a diseased skeleton In the latter case, we may deal with bones consisting of uncalcified osteoid tissue as in rickets. It is clear that these bones will not be able to withstand functional stresses and will become more or less deformed because of their increased *physical* plasticity Normal bones are, physically speaking, rigid and not plastic. With changes in functional stress, normal bones become

deformed because of their *biologic* plasticity. By coordinated resorption and apposition these bones assume, ultimately, the shape which they would have assumed if their plasticity had been physical.

Biologic plasticity is characteristic of bone tissue wherever found. The growing *skeleton has a much greater* adaptability to changes in form and function than does the adult skeleton. The reason for this difference is obvious. The final molding and the evolution of the structure of these bones proceed by patterned growth under the influence of normal function. A change in function leads in the growing bone to a change in growth pattern and the ultimate extensive changes in form and structure take place directly and in a relatively short time. In the adult skeleton, *reconstructive adaptation to abnormal function* occurs indirectly, more by structural changes than by changes in *form*. The structural changes sometimes give the impression of emergency changes. The reconstruction of an adult bone is always a lengthy process, often requiring years for completion.

The outline at the beginning of the chapter is an attempted classification of the *biologic processes of repair and adaptation of bones under abnormal conditions*. The term primary is intended only to signify that the changes so classified precede the adaptive changes of the bones.

PRIMARY CHANGES OF FORM

Deformities of the Diseased Skeleton

The deformities of the skeleton in severe cases of rickets, osteomalacia, *and osteitis fibrosa cystica generalisata* (Recklinghausen's bone disease) are *manifold* and generalized. Some of the more important changes will be mentioned in the discussion on rickets, for instance, the deformities of the pelvis, which may be an important consideration in childbirth. At this juncture, only one example will be discussed, namely, the adaptive changes in a long bone which has bent under normal functional stress. Such changes which occur mainly during the healing phases of the disease can be characterized briefly as an attempt of the organism to reinforce the curved bone against further bending or breakage (Fig. 107).

Progressive apposition of bone is observed at the concavity *of the shaft*. The compact layer is thus considerably *thickened at the concavity but is partly* resorbed from within and is replaced by spongy bone. A *uniformly large* marrow space does not exist in such bones. Instead, it is, to a variable *extent* replaced by functionally arranged spongy bone. The trabeculae radiate *from* the compact bone at the concavity to the convex surface. The compact bone at the convexity is, in many cases, considerably thinned. *In addition* to these changes, a flattening of the bone can frequently be observed *in the plane of curving*.

The changes described may be *regarded* as an adaptation to the change in functional stress after primary bending of the bone. The bending forces are most effectively resisted by material *that is* at some distance from the neutral axis; hence, the apposition of bone at the concavity and *formation* of a new

compact layer on this surface. When this reinforcement has been effected, the stress at the convexity is greatly reduced hence, the thinning of the compact bone at the convexity Despite the apposition of bone at the concavity the *bone is never straightened but remains a curved bone in which shearing* forces play an important role hence, the development of spongiosa which fills the marrow space The increase in one diameter by apposition of bone at the concavity permits the reduction of the other diameter which is at right angle to the plane of bending hence, the flattening of the bone

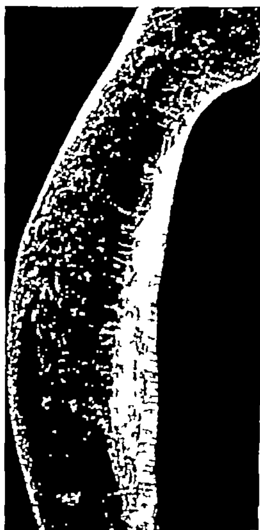


Fig. 10 —Functional reconstruction of a deformed rachitic femur Apposition of compact bone at the concavity Trabeculae radiate to the thin compact layer at the convexity (After W Putschar)

Observation of the changes described led Wolff and many others to the erroneous generalization that pressure stimulates bone apposition whereas traction causes resorption. Although the concavity in a curved bone is under pressure and the convexity under traction, shearing forces are responsible for the apposition of bone at the concavity and decrease in function is responsible

for bone resorption at the convexity Wolff's interpretation and the many ensuing controversies were based on a consideration of pressure and traction as two biologically opposed forces, one causing apposition, the other resorption, of bone It is recognized that pressure, as well as traction may under certain circumstances, cause formation as well as destruction of bone (see page 136)

Deformities of the Normal Skeleton

Primary deformities of the normal skeleton are due almost exclusively to trauma for example, fractures healing with fragments displaced The changes which adapt the deformed bone to the changed mechanical conditions

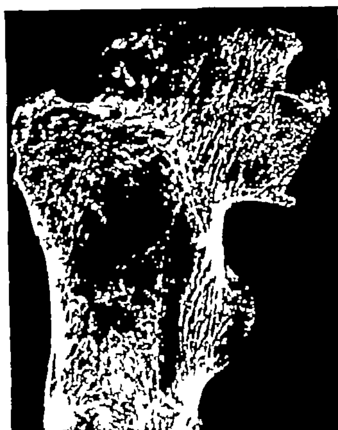


Fig 102.—Functional reconstruction of the proximal end of the femur after healing of a fracture which led t almost total loss of the neck. Note the nearly vertical direction of the trajectories. (After W Putschar)

are intricate, demanding analysis in each case. Generally speaking they consist of the more or less perfect reconstruction of the two fragments and the bony callus, a process which may continue for several years. Formation of compact layers in the callus, dissolution of compact bone of the fragments and its replacement by spongy bone and, finally creation of spongy trajectories*

* A definition f spongy trajectories as the systems of strengthened trabeculae arranged in the lines of stress is found on page 121.

are the essential features of this process. The reconstruction of the bone can be easily visualized in the fractured neck of a femur that has healed with so marked a shortening that it could almost be described as an elimination of the neck. In this case (Fig 108) the curved and intersecting trajectories of the head and neck are almost entirely replaced by steeply ascending rather straight trajectories arising in the medial compact bone of the shaft. Disuse has led to atrophy of that part of the head of the femur which lost its function because of rotatory displacement

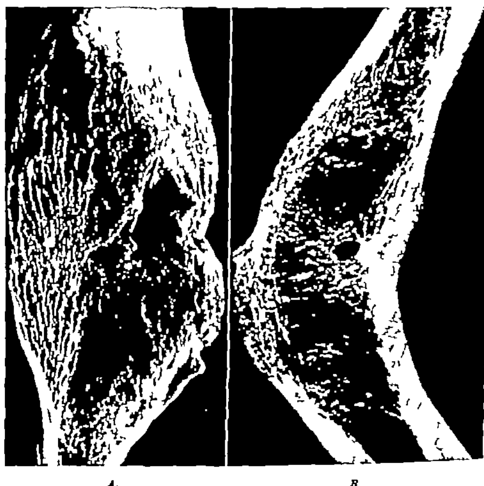


Fig. 109 —Ankylosis of the knee. (After W Putschar)
A. In extension.
B In flexion.
Compare the structure of compact and spongy bone.

PRIMARY CHANGES IN THE TOPOGRAPHIC RELATION OF BONES

Immobilization by Ankylosis

Immobilization of a joint by ankylosis leads likewise to adaptive reconstruction. The outcome depends largely on the position in which the ankylosis occurred The reconstruction is not complete for several years. In principle,

the changes in the bone can be described as a simplification of the architecture and an internal structural unification of the ankylosed bones The simplification of the structure is a direct consequence of immobilization which eliminates all those mechanical forces which had acted on the bones in positions different from that in which they became ankylosed. The unity is expressed in the continuity of the trajectories across the former articular space so that the fused bones are transformed into one structural element (Fig 109 *A*) The degree of influence exerted by the relation of the bones to each other can be visualized by examining the bones in ankylosis of the knee joint in a semi flexed position (Fig 109, *B*) The structure of compact and spongy bone resembles closely that of bones curved by rickets (Fig 107) The compact bone on the concave (flexor) side of the knee is greatly thickened mostly by formation of new compact bone in the fused articular ends, which normally do not possess a thick compact layer In contrast there is no continuous compact layer on the convex (extensor) side. The spongiosa trajectories radiate from the compact layer at the concave surface and end in the dense spongy layer on the convex surface These structural changes are again an adaptation to the curving of the bone which resulted from fusion of the femur and the tibia

Imbalance of Mechanical Forces

Coxa Valga.—Deformities from paralysis or spasticity of muscle groups are common, beginning with a more or less permanent change in the relation of the involved bones to each other in conformity with the altered function of muscles. An example often quoted is the muscular coxa valga (Fig. 110) characterized by an increase in the angle between the shaft and the neck of the femur The cause for this deformity is either a paralysis of the abductors or a spasticity of the adductors of the thigh. The main function of these two muscle groups is the shifting of the pelvis and trunk from the rest position to the side of the weight bearing leg during walking If the right leg is the weight-bearing leg and the left leg starts to swing forward, the body weight is transferred to the right leg by an inclination of the pelvis to the right by an action of the right abductors. These muscles act from the femur and tibia (via the iliotibial tract of the fascia lata) as the fixed points upon the pelvis. At the same time the right adductors act as a brake for this movement and are prepared, by further contraction, to initiate the swing of the pelvis to the left side when the left foot reaches the ground and the left leg becomes the weight bearer This alternate shifting of the pelvis not only transfers the weight of the body to the standing leg but also allows for the free movement of the swinging leg by raising the acetabulum on this side. In cases of imbalance of the abductor and adductor groups, in favor of the latter the active shifting and support of the body weight is impaired and overcompensated by an exaggerated leaning of the trunk toward the involved side when the impaired leg serves as the weight bearing leg (Fig. 111)

The resulting abnormal load on the head of the femur leads seemingly to overstress in the region of the neck with an increase of the bending and the

shearing forces The growing skeleton adapts itself to this overstress by straightening the angle between the neck and the *shaft* of the femur In the adult, similar disturbances do not lead to development of coxa valga, but to a strengthening of the compact bone at the medial surface of the neck, calcar femoris, and the proximal end of the shaft The *changes in the adult* are in structure rather than in form.

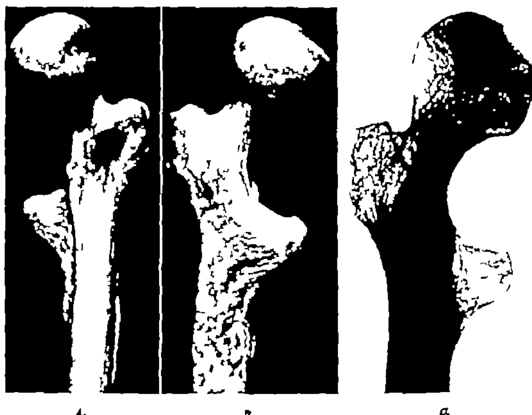


Fig. 110—Proximal end of the femur in paralytic coxa valga. (After Gg. H. Gruber from W Putschar)
A Anterior view
B Posterior view
C Anteroposterior roentgenogram.

Scoliosis—Another example of compensatory deformity of bones is the change in the vertebrae and ribs in scoliosis caused by paralysis of the dorsal muscles for example in poliomyelitis, syringomyelia, and other nervous disorders. Scoliosis, that is, lateral curvature of the spine, can also serve as an example of skeletal deformity caused by congenital malformation a habitual posture, and traction from scars.

Paralysis of the dorsal musculature leads to a lateral curvature of the spine the convexity of which is usually directed as could be expected, toward the paralyzed side but sometimes toward the normal side. The latter type deserves an explanation It is known that the lateral curvature of the spine especially in the thoracic region, is commonly associated with a rotation of the

vertebral bodies toward the convexity of the spinal curvature. It seems that the rotation of vertebrae may determine the direction of the spinal curvature in cases of imbalance of the right and left dorsal musculature. Normally the deep oblique muscles of the back (multifidus and rotatores) the most important rotatores of the dorsal vertebrae ascend from the transverse process of one vertebra obliquely to the spinous process of a higher vertebra During their contraction, the transverse process of the lower vertebra is held in posi-

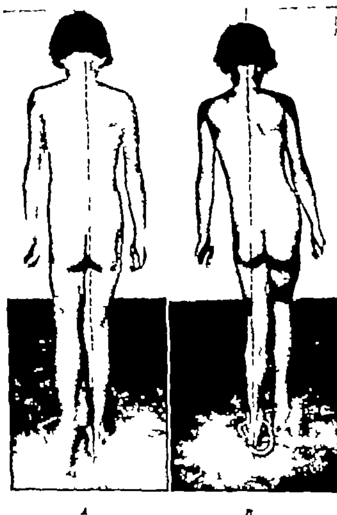


Fig. 111.—Position of trunk in paralysis of the left gluteal muscles. (After H. Storck from W. Putscha.)

A Right foot carries the weight.
B Left foot carries the weight.

tion by the long muscles, the erector trunci, and from here the rotatores act upon the spinous process of the higher vertebra rotating the vertebra to the opposite side The left rotatores therefore turn the vertebrae to the right side If this system of dorsal muscles is unbalanced by paralysis of the muscles on one side, the fixing component of the long muscles which acts mainly upon the transverse processes is lost The broad superficial muscles of the back the

latissimus dorsi, the trapezius, and the rhomboidei, fix the spinous processes firmly The rotatores then reverse their action and, instead of using the transverse processes as fixed points, act now from the spinous process upon the transverse process of a lower vertebra. Then the direction of their rotatory effect is also reversed that is, the left rotatores move the vertebrae toward the left side. In other words, paralysis of the right dorsal muscles may lead to rotation of the vertebrae toward the left side, the normal side, and thus initiate a scoliosis, the convexity of which is finally directed toward the nonparalyzed side. This paradoxical curvature of the spine is probably due to minor differences in involvement of different segments of the dorsal musculature which are entirely too complicated to permit of mathematical analysis.

Malformation which leads to lateral spinal curvature is, for the most part, due to unilateral development of supernumerary or lack of normal vertebral half bodies. Asymmetry thus caused will of course, lead to scoliosis, the convexity of which is found on the side which contains more segments. Posture habits, sometimes associated with certain professions, are frequently enumerated among the causes of scoliosis for instance, the position assumed in carrying weight on one shoulder or shifting of the body weight to one leg and standing in a laterally bent or twisted position. In these cases a combination of an symmetrical load and an asymmetrical muscle tension finally results in the adaptive and permanent spinal deformity

The scoliotic curvature of the spine can be caused also by traction from pleuritic scars. In these cases, the scoliotic convexity is toward the normal side.

In spite of these observations and in spite of the great volume of literature on this spinal deformity the pathogenesis of scoliosis is still controversial on many points The deformities of the single vertebra can be studied and satisfactorily explained by looking upon these changes as the direct consequence of a lateral curvature, whatever its primary pathogenic source.

The vertebra in scoliosis follows the law outlined before: Because of its biologic plasticity the vertebra, under abnormal forces, assumes the shape into which these forces would mold it if the bone possessed physical plasticity In the growing skeleton, the biologic plasticity can be visualized as a change of growth pattern so that the bone develops an abnormal shape. In the adult skeleton the changes are less direct. The normal shape of a bone is changed by abnormal apposition and resorption. Under the stimulus of abnormal forces a new bone, adapted in form and structure to the new function, is created.

Scoliosis, rarely affecting the entire spine, is in most cases partial and primarily confined to the thoracic part of the vertebral column. The adaptation of the body to this shift of its axis and center of gravity is the development of compensatory lateral curvatures. Most pronounced is the secondary scoliosis of the lumbar spine less pronounced, that of the cervical vertebrae. The secondary or compensatory scolioses turn the convexity in the opposite direction from the primary curvature (Fig 112)

ome of the adaptative deformities of the vertebrae and ribs are not yet stood. The principal distortions can be classified into two main groups caused by the changes in vertical load upon the vertebrae and interver i discs, the direct consequence of the lateral curvature, and those regarded ondary caused by the tension, mainly of muscles, caused by a shift of the

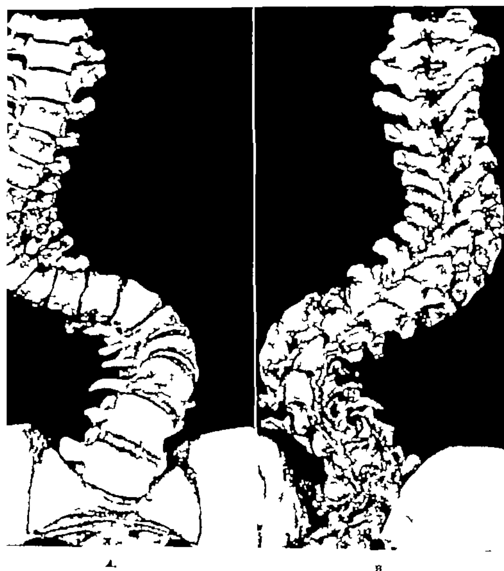


Fig. 112.—Typical S-shaped scoliosis. (After W Putschar)
A. A terior iew
B Posterior iew

iental skeletal parts from a symmetric into an asymmetric position. The ges in the first category involve mostly the vertebral bodies and inter ebral discs. Those in the second category are changes in the processes of vertebrae and in the ribs. All these changes can be briefly described as an npt to regain equilibrium.

The *normal vertebral column* shows the well known *sagittal and symmetrical* curvatures alternatingly convex anteriorly and posteriorly Adaptation of the segments is found mainly in the intervertebral discs. The vertebral bodies too are adapted to these curvatures, assuming either a wedge shape or leaning shape (Fig 113) In the wedge-shaped vertebra, the body is of different height anteriorly and posteriorly The thoracic vertebra, if wedge shaped, is higher posteriorly than anteriorly corresponding to the posteriorly convex kyphotic curvature of the thoracic spine. The body of a wedge-shaped lumbar vertebra is higher in front than in back, corresponding to the anteriorly con

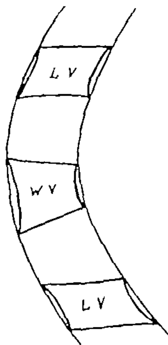


Fig. 113.—Diagram to show the two possibilities of adaptation in the shape of the vertebral body to the curvature of the spine. *L.V* Leaning vertebra *W.V* wedge-shaped vertebra.

vex, lordotic curvature of the lumbar spine. In a "leaning" vertebra, the body is of equal height anteriorly and posteriorly but the upper surface is shifted sagittally against the lower surface. The sagittal section of a "leaning" vertebra is rhomboid instead of rectangular The upper surface is, for instance, shifted posteriorly in relation to the lower surface in the lower thoracic spine in the upper parts of the thoracic spine, the upper surface is shifted anteriorly against the lower surface. These deviations from the "ideal" shape of a vertebral body are slight in a normal spine and are symmetrical.

The adaptative changes of the vertebral body of a scoliotic spine are, in principle, the same as those just described in the normal individual, but they are exaggerated and asymmetrical. The body of a scoliotic vertebra is therefore low at the concavity and high at the convexity of the lateral curvature. This type of vertebra, the wedged vertebra, is found at the height of the curvatures. In the transitional or oblique parts, the vertebrae lean over to that side

to which the vertebral column inclines and can be compared to short cyli with an oblique axis, the bases of which are parallel. Another way of de ing these leaning vertebrae is to say that the upper surface is shifted a the lower surface and parallel to it toward that side to which the part vertebral column is inclined.

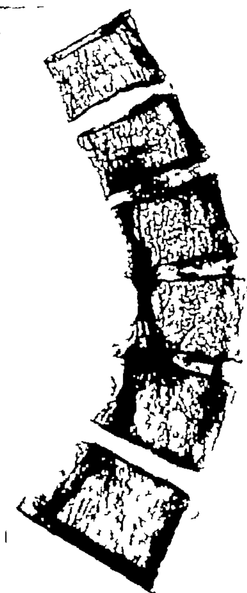


Fig. 114—Functional adaptation of the vertebrae in kyphoscoliosis. Note the re trajectories on th concavity (After M. B. Schmidt)

The architecture of the spongiosa is changed according to the mechanical stresses (Fig 114) The direction of the spongy trabecul trajectories conforms *generally* to the changed direction of the axis vertebral body In the wedge-shaped vertebra a second change

spongiosa has been observed Here, the forces of pressure are considerably increased in the low "compressed" part of the vertebral body at the concavity of the lateral curvature and the forces are reduced, as compared with the normal forces, in the higher parts of the body at the convexity In accordance with this shift in the load, the spongiosa shows signs of osteosclerosis in the parts of the body close to the concavity and signs of osteoporosis on the opposite side (Fig 84)

The adaptation of the vertebral body to the curvature of the spine is, in the normal and in the scoliotic spine accompanied by an analogous adaptation in form of the intervertebral disc. The disc is compressed and low at the concavity extended and high at the convexity The increased pressure at the concavity effects a shift of the nucleus pulposus toward the convexity The grooves at the cranial and caudal surfaces of the vertebral body which are due to the pressure of the nucleus pulposus shift with it from their central position toward the convexity A change in the course of the fibers and fibrous plates of the disc from vertical to oblique is said to be a proof of an actual shift and rotation of two adjacent vertebrae.

In all discussions of the skeletal changes in scoliosis, "convex rotation" plays a prominent part. In a scoliotic spine, the vertebrae seem to be turned toward the convexity of the curvature. In Fig. 112 the thoracic vertebrae seem to be rotated toward the right side, the lumbar vertebrae toward the left. In Fig 115, a line was drawn along the alleged midlines of the vertebral bodies and here, too the convex rotation is striking The explanations offered for this change in position and shape vary considerably, all however attribute the cause to abnormal pressure or tension acting upon the vertebra from the transverse or spinous processes.

It seems that such forces are responsible only for the actual rotation which takes place in the thoracic spine. This rotation is limited, the movement being arrested mainly by the tension in the intervertebral disc which is undergoing torsion. From then on, the rotating forces will tend to cause deformation of the processes of the vertebral bodies because bone is so much less resistant to abnormal stress than is connective tissue. If actual rotation is limited in the thoracic spine, it is practically nonexistent in the lumbar spine. The difference is due to the different positions of the articulating facets of the dorsal and of the lumbar vertebrae In the thoracic vertebra, the articulating surfaces are arranged in a dorsally convex plane so that the axis of rotation is found inside the vertebral bodies and intervertebral discs which are the parts of the spine least movable in the sense of rotation. In the lumbar vertebrae, the plane of articulating facets is dorsally concave and the axis of a rotatory movement would be located in the roots of the spinous processes. The vertebral body would in rotation be the part of the vertebra showing the greatest amplitude of movement. Such movement is, of course, impossible and, therefore, rotation is almost nonexistent below the thoracic portion of the vertebral column.

The change in the vertebral body which imitates the far reaching convex rotation has long been recognized as a deformation of the bone achieved by growth changes. These growth changes are plainly evident in the child by the

asymmetric position of the epiphyseal plates between vertebral body and arches. The plate corresponding to the concavity in scoliosis is situated farther forward or deeper in the body than the other It can be shown that, in this case, the 'concave' half of the arch grows faster than the convex half.



Fig 116.—Rotation of the vertebrae in scoliosis. The anterior midline has been marked (After W Putschar)

Thus, the vertebral body is literally shifted toward the convex side a shift which could be called growth rotation. After closure of the epiphyseal plates, which occurs around the fifth year the convex rotation is effected by correlated apposition and resorption of bone

The shift of the load bearing bone of the vertebral body toward the convexity seems to be caused by the fundamental change in vertical stresses in scoliosis. A curved segmented column which carries a vertical load is in equilibrium if the plane of curvature and the plane of symmetry coincide in other words, if the load bearing material is distributed symmetrically to the plane of curvature. This is the case in the normal spine which is curved in and symmetrical to the midsagittal plane. A lateral curvature will, of course, destroy this optimal relation, the plane of symmetry and plane of curvature being at right angles to each other the curvature is in a frontal or a coronal plane; the symmetry is still to the sagittal midplane of each vertebra. Following the law of functional arrangement of bone the tendency to re-establish optimal conditions will work toward a new distribution of bone material. The ultimate goal would be a vertebral body symmetrically built in regard to a frontal plane, the plane of curvature. The actual changes never will go as far as that. As a consequence, the scoliotic spine remains unbalanced and secondary changes, as, for instance, degenerative changes of the disc and spondylolisthesis and gliding dislocation of a vertebra, are the consequences.

In order to understand the other complicated changes of vertebrae and ribs, it is necessary to visualize the disturbance in equilibrium of the forces acting upon each skeletal segment. Much has been said in the literature on the rotation shifting and bending of parts of the vertebrae. Such terms, although they may shorten and seemingly simplify the description, should not be used without stressing the fact that all these changes are not physical but are brought about by the process of growth in the young and the old. This not only would prevent a misinterpretation of the biologic processes which are active during the changes of the skeleton, but would also emphasize the necessary slowness of such changes.

The forces called forth by the lateral deviation of a vertebra are roughly divided into vertical and horizontal. The vertical forces are elicited by the obliquity of the segment in its lateral position, an obliquity that is opposite, below and above the summit of a lateral curvature. Below the height of a right lateral curvature, the transverse axis of a vertebra is oblique from left and above to right and below In the upper part of the arch the axis is directed from left and below to right and above. In the first stages of the development of a scoliosis, the transverse processes and ribs are oblique to the vertical axis of the body On the convex side transverse processes and ribs diverge on the concave side, they converge. The abnormal tension of the intercostal muscles on one side and of the elevators* and depressors† of the ribs on the other side, tends to change the position of the transverse processes and ribs in such a way that they resume as nearly as possible, a horizontal position. In the beginning in a lateral curvature, the transverse processes and the ribs are still in their normal relation to the respective vertebra in other words they are arranged sym

*Scaleni muscles and, indirectly trapezius and sternocleidomastoid muscles in conjunction with subclavian muscl

†External and internal abdominal oblique muscles, recti abdominis muscles, and quadratus lumborum.

metrically in regard to the vertebral bodies In later stages when they again approximate a position horizontal in space or to the vertical axis of the entire body they change their relation to the respective vertebra transverse processes, for example, are asymmetrically and obliquely placed to the vertebral body In a case of scoliosis, if we look at an isolated thoracic vertebra taken from the lower half of the lateral curvature, the convex transverse process seems to be bent upward the concave bent downward. In a vertebra taken from the upper part of the scoliotic region, these relations are reversed. The vertebra at the height of the lateral curvature shows an almost symmetrical structure, the asymmetry increasing with the distance from this point. All these changes are duplicated to some extent in the lumbar spine but are there of lesser degree.

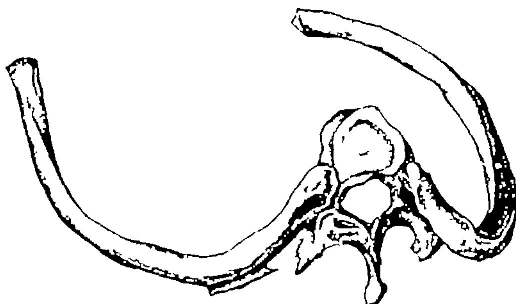


FIG. 116.—Vertebra and ribs from a case of scoliosis the con exity faced right. (After Lorenz.)

In scoliosis the lateral displacement of the single vertebra through symmetrical tension of muscles and ligaments leads to a typical change in the ribs, more pronounced on the side of the convexity than on the opposite side. This change finds its most striking expression in a more acute bend of the 'convex rib in the region of the costal angle. At the same time the neck of the rib is pushed posteriorly against the respective transverse process. The opposing changes taking place in the concave rib are always less pronounced. The posterior prominence of the ribs on the convex side is a striking feature of the exterior of a scoliotic individual. The pressure of the rib upon the transverse process causes correlated apposition and resorption so that the process seems to bend backward (Fig 116)

Under the force of their heavy musculature, the spinous processes in scoliosis tend to be pulled toward the midline in other words, to the side of the concavity of the curvature. The bone under asymmetrical tension reacts by resorption and apposition so that the entire spinous process or its terminal part seems to bend toward the midline. Here again, the balance of forces in each individual and in the different segments in one individual seems to vary considerably according to the complicated arrangement of the deep muscles of the back.

Under no circumstance should the position of the spinous process be evaluated by studying its relation to the body of the same vertebra because this body is deformed and a so-called midline is merely imaginary Failure to observe this precaution is responsible for many conflicting statements in the literature.

The unbalanced stresses upon the vertebrae are manifest also on the articular processes which are generally atrophic on the convex side. The concave processes which are under greater pressure are strong and the articular cartilage thick Corresponding differences can be seen also in the articular capsule, which is thicker and denser on the concave side The increased and distorted stresses on the small articulations of the vertebral column lead in most cases, to traumatic arthritis.

Permanent Dislocation of Joints

Of special interest are the adaptive changes of bones following unreduced dislocation of joints. Here a more or less successful attempt to form a new articulation is observed Almost all reported cases deal with the development of a new socket for the dislocated head of the humerus or femur Congenital and traumatic dislocation of the hip joint is most frequently the cause of such changes. In well-developed nearthrosis, the principal changes are the formation of a groove in the bone with which the head of the femur is in contact the development of exostoses from the border of this groove deepening the newly formed socket and, finally changes in the cartilaginous covering of the femur head and, sometimes, the development of cartilage in the abnormal socket.

Biologically the development of a new socket for the dislocated convex articular body seems to be the effect of a combination of pressure and tension Pressure is probably responsible for the initial hollowing out of a bony groove If, later a certain amount of mobility is achieved, the connective tissue around the dislocated bone will be under traction, which will soon lead to a degree of functional organization. The transmission of the more or less regular tension to the borders of the nearthrotic groove will be responsible for the formation of new bone enveloping to a certain degree the convex articular head

Pathologic Relaxation of Ligaments

Pes Planus.—An example of skeletal changes caused by or accompanied by relaxation of ligaments is the deformation of the tarsal bones and those of the leg in pes planus (flatfoot) The discussion cannot go into the confusing variability of clinical symptoms rather it will be kept on more general lines.

Whether the breakdown of the longitudinal and transverse arches of the foot is the result of a primary deficiency of ligaments or muscles is highly controversial. Without trying to minimize the role of ligaments in maintaining the relation of the tarsal bones to one another the inadaptability of ligaments has to be stressed A ligament is generally built with a wide safety margin that is, it can withstand considerable stresses above the average However once overstretched, it cannot resume its original length which is necessary for normal function. This is, of course, a consequence of the inelasticity of the collagenous fibers, the structural elements of a ligament. A muscle, though its

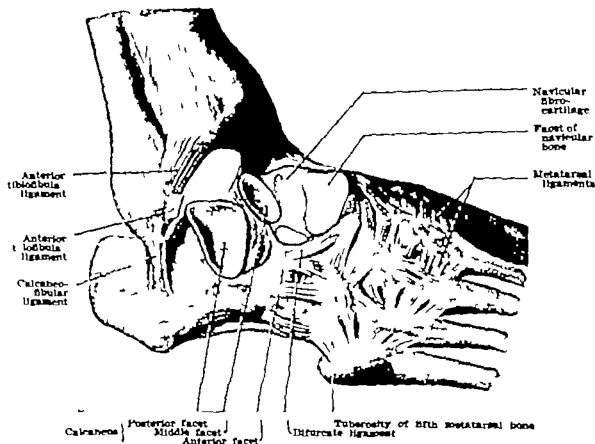


Fig 117.—The articulating surf ces of the lower talar articulation. Note the participation of the navicular fibrocartilage in haping the socket for the head of the talus. (After Tandler)

elements likewise are not elastic in a physical sense, is readily adaptable in length by changes in its contraction These changes in muscle tonus could be designated as physiologic or biologic elasticity Muscular activity and muscle training have always been emphasized as therapeutic measures in incipient or moderate pes planus which confirms their function in preserving the normal shape of the foot. The muscles which seem to play the most prominent part in maintaining the normal shape of the foot are primarily the flexors of the toes the two tibial muscles, anterior and posterior which act as supinators, elevat

ing the inner border of the foot and, finally most of the short muscles of the sole, especially the abductor hallucis, the volume of which cannot be understood if we do not realize its action in maintaining the medial longitudinal arch of the foot.

The skeletal changes in advanced flatfoot are twofold changes in position and in shape of the involved bones

The principal change in pes planus seems to be the breaking down of the anterior talotarsal articulation. This joint is the weak point in the architecture of the human foot. The head of the talus articulates here with the calcaneus, resting upon the sustentaculum tali, the navicular bone, and the navicular fibrocartilage or calcaneonavicular ligament (Fig. 117) The fact that a ligament, however strong, forms part of the socket for the head of the talus explains the relative insufficiency of this joint which is under severe vertical stress. Mechanically the talus acts as a wedge, trying to force the calcaneus and navicular bone apart As long as the powerful and adaptable muscles, especially the anterior and posterior tibial flexor hallucis longus, and abductor hallucis muscles, carry part of the load, the calcaneonavicular ligament will be able to withstand the pressure exerted upon it by the head of the talus.



Fig 118.—Skeleton of the foot in extreme *pes planus*. (After W Putscher)

A pathologic relaxation of the calcaneonavicular ligament, which could be termed the key ligament of the human foot, permits the talus to sink between the calcaneus and the navicular bone and thus to slide downward and medially from its position upon the calcaneus. During this movement, the calcaneus turns over as a chair might if the person sitting on its edge slides to the ground The movement of the calcaneus is a medial rotation or pronation (Fig 118)

The loss of normal relation between tibia and fibula and tarsal bones and between the single tarsal bones necessarily leads to changes in the shape of these bones. These changes are effected by resorption and apposition of bone which mold the bone just as if it had physical plasticity Where articular cartilage is involved in such processes, the changes are of an entirely different nature. Under greater pressure or after loss of function, articular cartilage is

not resorbed but degenerates, leading to the symptoms of a degenerative arthritis, and the new cartilage that is formed is not hyaline but fibrous These changes play a very prominent role in the development of pes planus (flatfoot)

The most striking changes in the shape of the involved bones can be observed in the tibia and fibula, talus and calcaneus. Minor changes occur in the navicular and cuboid bones, whereas the cuneiform and metatarsal bones generally escape significant changes.

In sliding downward and medially the head of the talus deviates farthest so that the talus as a whole rotates medially around the vertical axis through its body In other words, the talus is forced into an adducted position Since such a movement is opposed by the tightly fitting malleolar arch any force acting in this direction must cause changes in the malleolar areas of the tibia and fibula in the sense of a medial rotation. This is finally effected by a shift of the fibular malleolus anteriorly and of the tibial malleolus posteriorly Thus, the tibia itself finally shows a medial torsion of its lower end, which is the reverse of the normal lateral torsion. If a normal tibia is placed in such a position that the longest diameter of its proximal end is in a frontal plane, the longest diameter of the distal end is laterally rotated. The angle of rotation varies considerably and is, in most individuals, between 5 and 20 degrees. During the breaking down of the arch of the foot, this lateral torsion is reduced or even reversed to a medial torsion.

The adductory movement of the talus against the tightly fitting tibiofibular arch causes the head of the talus to 'bend' against its body by changes in the shape of its neck. The axes of body and head may form an angle of from 20 to 30 degrees. The anterior portion of the articular facet of the talus loses contact with the crural socket with the result that the anterior one-fourth or even one third of the trochlear cartilage finally degenerates. The medial and lateral malleolar facets of the talus undergo partial degeneration. The posterior portion of the fibular and the anterior portion of the tibial cartilage may break down as a result of the medial rotation of the malleoli. The latter changes are not quite constant because of the difference in relative position of the tibia and fibula and the talus.

The articular facet of the head of the talus changes considerably because the head turns so far medially and downward that most of its convexity is now in contact with the elongated tibionavicular ligament whereas the neck of the talus makes contact with the lateral part of the navicular bone. The extension of the articular facet to the lateral surface of the neck gives the impression that the neck of the talus has disappeared. The inferior facets of the talus, especially the one articulating with the sustentaculum of the calcaneus, also undergo significant changes, principally as a consequence of the medial and downward shift of the talus against the calcaneus.

The most important changes of the calcaneus are as follows the sustentaculum tali is greatly enlarged jutting out medially and its upper surface faces more or less anteriorly corresponding to the medial and downward

movement of the talus. The superior facets of the calcaneus often sho siderable change in that they extend over part of the tarsal sinus, w other areas of the articular cartilage degenerate. The anterior facet calcaneus articulating with the cuboid bone is often extended superi laterally onto a bony projection because of pronation of the calcane part of the articular cartilage at the inferomedial corner may degenera result of the changes in position of the calcaneus.

The navicular bone is sometimes altered by the pressure of the h the talus to a more nearly wedge-shaped body. The edge of the wedg stitutes the upper and outer parts, where the pressure of the talus in its ward and inward movement is greatest. The base of the wedge is the and lower part of the navicular bone.

The cuboid bone shows, in most cases, only slight deformities, whic resent an adaptation to the pronatory rotation of the calcaneus. The cal facet of the cuboid is often extended upward onto a bony ridge whi developed by apposition of new bone.

PRIMARY CHANGES OF MECHANICAL STRESSES

Increase in Function

The effect of quantitative changes in mechanical stress upon the bo easily understood. An increase in normal pressure and traction as, f stance in strenuous physical labor or exercises, seems to lead to a localized or to a generalized strengthening of the skeleton. Little is k about these changes beyond the fact that the bones as a whole seem heavier and processes, crests, and ridges serving as attachments of m are enlarged, greatly strengthened, and of a peculiar roughness. It wo wrong to conclude from these observations that traction acts as a s stimulus in apposition of bone. The pressure bearing bones or parts of are likewise *reinforced by the production of new bone*, a fact which obvious and therefore often unrecognized. The reaction of the skeleton i case proves the contention that the increase of any physiologic stress i limits of tolerance acts as a growth stimulus on bone.

Lack of Function

Decrease of the functional stresses leads to atrophy of the skeleto striking example of disuse atrophy can be found in the changes in bone st after amputation (Fig. 119). The peripheral end can atrophy until the tapers to a point. The compact cortical layer is thinned considerably in the mal parts *mostly by resorption from within* and replacement by spongy The spongiosa shows the typical signs of osteoporosis, that is, the trabecul less numerous and thinner than normally. The picture is always compli by some changes in the external shape of the bone because of the unavo qualitative changes in functional stress after partial loss of the muscles a upon the bone.

Disuse atrophy of an amputation stump is in a degree dependent also on whether an artificial limb is worn. This fact is especially important after amputation of the leg. The end of the stump shows less reduction in circumference if an artificial leg is used although osteoporosis is marked. In some cases hyaline cartilage is formed on the pressure-bearing parts of the bone, and the soft tissues covering the stump may be separated from the cartilage by a synovial bursa.

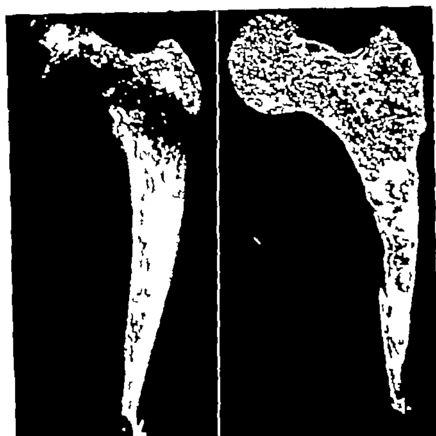


Fig. 118.—Disuse atrophy of the proximal part of the femur after amputation. (After M. B. Schmidt.)

The differentiation of hyaline cartilage in such cases, as well as in cases of pseudarthrosis, has been widely discussed. The consensus of opinion is that the differentiation of cartilage is caused by a combination of pressure and friction or a gliding contact. The fact that the avascularity of hyaline cartilage renders it capable of transmitting pressure to bone raises the question as to whether its differentiation may not be induced by changes in the blood vessels in the pressure area. These changes must necessarily be so balanced that impairment of the circulation results with ensuant transformation of connective tissue into cartilage without causing necrosis and resorption of bone. The range of such changes is understandably narrow so that the formation of ectopic cartilage can be considered an exception rather than the rule.

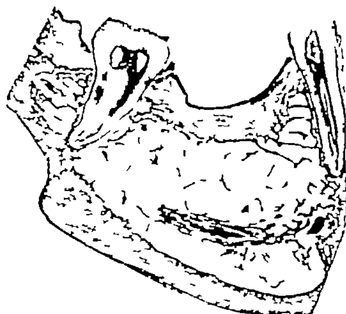
In paralysis of the brachial plexus from birth injuries, the entire arm is shortened. It is, however, questionable whether this inhibition of growth is due to the total or almost total lack of function of the paralyzed arm. The possibility that the atrophic, fibrosing muscles mechanically prevent lengthening of the bones has at least to be considered. That slight impairment of function inhibits growth has never been proved. Therefore the hope to stimulate undersized skeletal parts, for instance an underdeveloped mandible, by muscle exercises is nothing but a hope. It is probable that muscle exercises make a bone stronger but fail to make it longer.



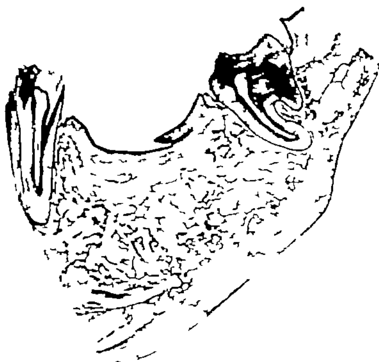
FIG. 120.—Sagittal section through the left lower jaw of an individual forty-two years old. Note the structure of spongy bone (supporting bone of the alveolar process).

An excellent object for detailed study of the changes in bone after elimination of function is the jaw. Here several stages of disuse atrophy can be recognized. The first of these stages is evident in the bone surrounding a tooth which has lost its antagonists. The loss of function is, in such cases, never total, and the remaining function is sufficient to prevent resorption of the alveolar bone proper. The supporting bone around the socket of the tooth is greatly reduced; in other words, the alveolar process shows typical signs of a localized osteoporosis.

The second stage of a localized disuse atrophy can be observed after loss of one or several teeth. The process is complicated because the atrophic changes are preceded by a regenerative period. In the period of regeneration, the empty socket or sockets are filled with new immature bone comparable to



A



B

Fig. 121.—Sagittal sections through the left and right lower jaw of an individual thirty nine years old.

A. Left side no upper molars present. Far-reaching disuse atrophy

B. Right id upper molars present. Disuse atrophy less advanced.

a bony callus developing after a fracture (see page 332) Much later after a few months to a year and more, reconstruction commences. In this period, the following changes take place

1. Gradual resorption of the immature bone of the callus and its replacement by mature bone.

2 Resorption of the lamina dura and its replacement by spongy bone, the trabeculae being orientated according to the changed function.

3 Resorption of a variable amount of alveolar bone beginning at the surface of the bony scar

4. Formation of a compact lamella at the surface, sealing the marrow spaces of the spongy bone

The details of this process of reconstruction and involution are dependent primarily on the presence or absence of functioning teeth bordering the edentulous area. As long as function is maintained in the neighborhood, the spongy bone shows a definite functional arrangement, the trabeculae extending horizontally for the most part. The leveling of the alveolar process is moderate and the compact lamella at the surface fairly strong If the loss of teeth is extensive or if the teeth bordering the edentulous area have lost their function, for instance, through the elimination of their antagonists, the osteoporosis is much more severe and the loss of bone substance at the alveolar ridge is much greater (Figs. 120 and 121)

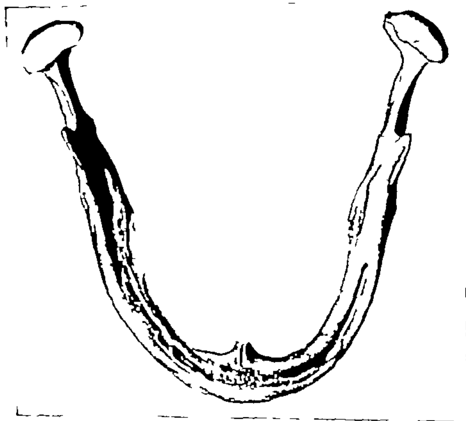
The reconstruction of a localized edentulous area is further complicated in the upper jaw if it falls within the extent of the maxillary sinus. Osteoporosis in such areas is, at least in part, caused by an extension of the maxillary sinus which hollows out the primary bony scar from within so that finally the alveoli of the two teeth bordering the extraction area are connected only by a relatively thin compact plate of bone The almost total elimination of spongy bone in the edentulous area of the maxilla is, of course, in conformity with the specific mechanical construction of the maxilla (see page 131)

The most extensive disuse atrophy of the jaws is found after total or *nearly total loss of the teeth. If all the teeth have been lost* and no denture is worn, the entire alveolar process gradually is resorbed. The atrophy may even involve parts of the maxillary and mandibular body In the maxilla, the subnasal parts may be completely lost The floor of the nose (palate) and the floor of the maxillary sinus may be reduced to paper thin plates of bone and may even show defects (Fig 122) In the mandible, the resorptive process may encroach on the mental foramen until it comes to lie at the upper surface of the thin body In extreme cases, a part of the mandibular canal may be exposed at the upper surface of the mandible (Fig 123)

The consecutive atrophy of the masticatory muscles in old edentulous people, after many years of decreased function leads to changes in the region of the mandibular angle. Resorption of bone at the posterior or inferior border of this region, that is, in the area of insertion of the masseter and internal pterygoid muscles, causes necessarily an increasing obtuseness of the mandibular angle.



: 122.—Extreme atrophy of the uppe jaw after total loss of teeth. Maxillary sinus opened by atrophy of its floo (After M. B. Schmidt.)



ig. 1[illegible].—Extreme atrophy of the mandible after total loss of teeth. Mandibular canal exposed. (After E. Greiner from H. Sicher and J Tandler)

The loss of the entire alveolar process and sometimes parts of the body of the upper and lower jaws leads to a relative prominence of the nose and the chin, which is increased by the sinking in of lips that have lost their support. Thus, the typical and well-known picture of the senile face develops (Fig 124)



Fig 124—Typical face of an edentulous woman. Relative prominence of nose and chin caused by the sinking in of lips and cheeks.

Effect of External Forces

Cultural Customs.—The biologic plasticity of bones is well exemplified in those instances in which external forces are employed to mold the growing bones according to some ideal fixed in cultural tradition. The deformity of the foot of Chinese women, the so-called 'golden lily' and various deformities of the skull, and, therefore, of the head, fall in this category. In both cases, force is exerted by the application of bandages in the growing individual, and it can be said that the bones are compelled to grow into an abnormal shape.

The changes of the Chinese foot were twofold. The four outer toes were forced under the sole so that the anterior part of the foot assumed a triangular shape. The longitudinal arch of the foot was increased in its curvature to the maximum so that the posterior part of the calcaneus was brought almost in line with the tibia and fibula and the toes pointed sharply downward. These changes were gradually effected by bandaging starting at about 5 years of age and continued throughout life, although the desired deformity was generally reached at 15 years. The deformities of the bones, which are visualized in Fig 125, can

not be better characterized than by the statement of Perthes, that they are changed in shape as if they consisted of a plastic material. It may be mentioned that as a result of the deformity there was a decrease in functional stress, leading to diffuse atrophy evidenced in slenderness and osteoporosis of the bones of leg and foot

Deformation of the head in infancy because of a fixed position of the infant, in other words, involuntarily or from application of bandages has been practiced at one time or another in almost every part of the world. This custom was observed in the Americas and Islands of the South Sea and in some parts still prevails. The desired shape of the head varies from a short and broad to a long and



Fig. 125.—Roentgenogram of the deformed foot of a Chinese woman thirty two years old. (After H. Virchow)

narrow head the former often associated with a protruding the latter with a receding forehead The appliances had in common the action of an external force upon the growing skull. It is of interest to note that brain volume, mental ability and duration of life were not influenced although the brain, under pressure assumed an abnormal shape (Figs. 126 and 127)

The deformities described were regarded by some as a consequence of a physical or passive plasticity of the growing bones. Others deducted from these observations that the law of functional adaptation of the bones was in

valid. It has been emphasized that the plasticity of the bones is the effect of an active biologic reaction to applied forces and, therefore, the effect of a modification of normal apposition and resorption. To conclude that functional stresses have no decisive influence on the shape and structure of a bone because external and artificial forces exert a molding effect is absurd. On the contrary the molding influence of external force is but additional proof of the important role that mechanical stress plays in the life of the skeleton.



Fig. 126.—Artificially deformed skull from the Bismarck Archipelago. (After R. Martin.)

Habits.—Deformities of bone resulting from a habitual position of the body or habitual activities are still under discussion. For instance, the question as to whether the habitual position of an infant has an influence upon the development of the skull in a dolichocephalic or brachiocephalic pattern has not yet been decided. An inhibitory influence upon the growth of the mandible is seen by some authors in children's habit of sitting for hours with the chin cupped in the hands so that the weight of the head exerts pressure in the temporomandibular articulation This pressure allegedly is injurious to the condylar growth center

Changes in the jaws due to thumb sucking and similar habits are better known. The changes are entirely comparable with those resulting from orthodontic appliances since the abnormal forces act primarily on the teeth and are

then transmitted to the bone. Changes in the bones are restricted almost entirely to the alveolar process, which, in the upper jaw protrudes and in the lower jaw retrudes.

Therapeutic Appliances.—Changes in the jaws under orthodontic treatment have been studied extensively both clinically and histologically It is, of course, impossible to enter into a discussion of all the controversial questions



Fig. 127—Koslmo woman with artificially deformed head. (American Museum of N tural History New York.)

in this field The description has to be restricted mainly to the reaction of the alveolar bone proper and the supporting alveolar bone during an application of force upon the tooth.

As an example may be taken an upper incisor upon which a force acts, tending to move the crown labially (Fig 128) Experiments have shown that a tooth, under such a force, is tilted that is, the crown moves labially the apex of the root lingually In other words, the tooth rotates around a horizontal mesiodistal axis passing through the middle of the root. In some areas

the moving root exerts pressure upon the alveolar bone, in others, traction by stretching the principal fibers of the periodontal membrane. In the cervical half of the root, the area of pressure is the labial wall of the socket the area of traction, the lingual. In the apical part of the root pressure and traction areas are reversed.

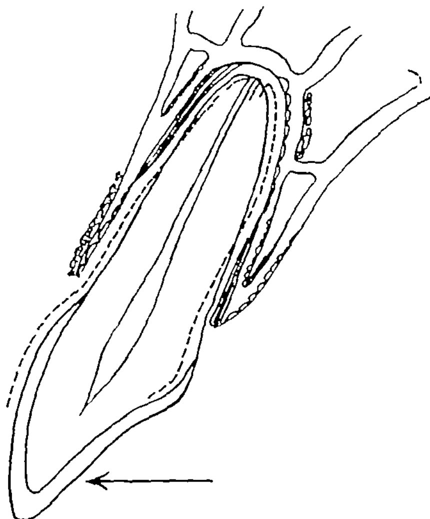


Fig 121.—Diagrammatic longitudinal section through an upper incisor and the surrounding bone. The tooth is being moved in the direction of the arrow Changes in the bone are indicated. Parallel lines, apposition of bone scalloped lines, resorption of bone stippled areas, osteophytic bone formation.

The reaction of the bone to these changes in mechanical stress is largely dependent on the strength of these forces. If they are too great, the periodontal tissues are destroyed in the pressure area and the adjacent bone necrotizes *and later is removed by undermining resorption.* Too great a traction can lead to quite similar injuries by tearing the principal fibers of the periodontal membrane and by injuring the blood vessels so that here also parts of the alveolar bone are necrotized. The results of application of too great and hence unbiologic force were cited as proof of the fact that excessive traction may lead to resorption of bone (see page 138)

If the applied forces are within the limits of tolerance, the reaction of the tissues is osteoclastic resorption in the pressure areas and regular apposition of bone in the areas of traction. In this way the bone not only makes room for the moving tooth but also follows it hence the expression that the socket shifts with the shifting tooth.

For an understanding of the biology of bone tissue and cementum is is of great interest that there is an evidently narrow range of pressure that on the one side stimulates the differentiation of osteoclasts and, therefore resorption of bone while it does not damage cementoblasts or osteoblasts that continue in their function of appositional growth Proof for this fact can be seen in marrow spaces which show apposition on one resorption of bone on another wall.

It may also be said that in the study of the behavior of bone under forces of pressure and tension the changes of the alveolar bone are extremely revealing because here as nowhere else these forces can be finely controlled in strength and time

These changes in the immediate vicinity of the tooth are only one phase of the reconstruction of the alveolar process. If resorption has progressed to a certain degree the supporting bone will also be involved. In the example chosen, the consequence of such a weakening of the alveolar plate on the labial side in the cervical area, and of some spongy trabeculae on the lingual side in the apical area causes compensatory apposition of bone on the surfaces away from the tooth If the resorption proceeds slowly apposition of bone, proceeding at the same rate, is characterized by the formation of layer upon layer of lamellated bone. Thus, the thickness and resistance of the bony lamellae which are resorbed from one surface are maintained by apposition on the opposite surface. If the speed of resorption exceeds a certain limit, the apposition of lamellated bone in layers is too slow to keep pace with the loss of bone substance. Then, what could be called an emergency reinforcement is provided by the development of osteophytes. Consisting of immature bone and arranged as spongy bone, osteophytes develop very fast. The probable stimulus for formation of the osteophytes is the distortion of a weakened part of the bone under stress The osteophytes commonly arise at right angles to the bony surface and are connected with one another by trabeculae or plates parallel to the surface of the bone (see page 136)

A reversal of this process can be seen in such areas where bony plates or trabeculae are thickened by apposition on one of their surfaces If this addition of bone has progressed to a certain degree, resorption on the opposite surface tends to restore the original dimensions of the bone

Experience with appliances which exert an upward and backward pressure upon the mandible by connecting a skull cap with a chin cap tends to show that it is possible to exert an inhibitory effect upon the growth of the mandible This is achieved by transmission of the forces to the temporomandibular articulation and thus to the condylar cartilage of the mandible, the growth center of the lower jaw That pressure upon a growing cartilage

should check its growth may at first seem to contradict the adaptation of cartilage to pressure bearing However the condylar cartilage has a unique growth mechanism because it grows in thickness not by interstitial, but by appositional growth (see page 108) The appositional growth is dependent on the vitality of the connective tissue covering the cartilage and it may well be that undue pressure upon the connective tissue decreases or prevents its contribution to the growth of the cartilage Connective tissue is, in contrast to cartilage not well adapted to resist pressure

Many orthopedic appliances are in use to correct deformities of the skeleton Tension and pressure are employed much as if they could reshape a plastic material but it is clear that we deal here with the same biologic reaction of the bones to therapeutic forces which results in deformities under the influence of abnormal stress in other words, not with a passive physical but with an active biologic plasticity

Unfortunately there are no satisfactory findings as to the details of such orthopedic treatment Ways could be found to study changes of the bones experimentally for instance, by producing deformities in a rachitic animal when its bones are pliable and then, by applying orthopedic treatment after healing of experimental rickets.

CHAPTER V

THE INFLUENCE OF ENDOCRINE GLANDS ON BONE AND BONES

INTRODUCTION

Normal development growth, and function of the human body orderly in time and space and genetically determined, is, to a high degree safeguarded by the system of ductless, or endocrine glands, the glands of internal secretion These organs elaborate specific products which are secreted into the blood stream and thus are carried from the place of origin to all parts of the body These products are called hormones because they 'set in motion cellular activities in distant organs. It should be emphasized that the hormones acting as catalysts do not always stimulate but sometimes inhibit the activities of cells.

This general description of endocrine activity permits of two important clusions. First, since hormones are transported to all parts of the body clear that the presence of one hormone may influence the activity of one or of the other endocrine glands. This interaction of the ductless glands is k as endocrine balance and it is this interaction which has made the stud endocrine function extremely difficult, since any interference with one o glands, for example, its experimental removal, influences other componen the endocrine system at the same time

The second important fact to be kept in mind is that the blood st furnishes the means of transportation for the hormones. Thus, we can u stand that hormone therapy is most effective when the hormone is injected is recognized, in fact, that there are only a few hormones which can act if g orally for instance extracts of the sex glands or gonads and of the thy

The fact that hormones do not show any specificity in different mam has made possible the use of hormone therapy on a large scale by administr of extracts of nonhuman organs, mostly of cattle and sheep Some of the mones have been successfully synthesized for example, the sex hormones. use of these synthetic products is far preferable to the use of organ extr which contain more than the active hormone.

Disturbances of endocrine balance are caused chiefly by quantitative cha in certain hormones. Whether qualitative changes in hormones occur is questionable. An overproduction of a hormone is caused by hypertroph hyperplasia of a ductless gland or by a tumor from proliferation of the f tional elements of the gland. Deficiency in the production of a hormo caused by atrophy or degeneration of the glandular cells. It is importan realize that destruction of the glandular elements may also be caused by a tu of the gland if the interstitial elements of the gland proliferate or a metas tumor arises in the gland In rare cases, there is congenital aplasia o endocrine gland for example, the lack of the thyroid gland in cretins.

The endocrine glands which are known to influence bone and bones

1 The hypophysis cerebri, or pituitary gland.
2. The thyroid gland.
3 The sex glands or gonads.
4 The parathyroid glands.

HYPOPHYSIS CEREBRI (PITUITARY GLAND)

The hypophysis the appendage of the brain, which is situated in hypophyseal fossa or sella turcica of the sphenoid bone, consists of two pri pal parts, the oral and the neural hypophysis. The latter develops from floor of the diencephalon behind the optic chiasm Its connection with brain persists as the hypophyseal stalk The oral part develops as an epithe pouching on the roof of the primary ectodermal oral cavity (Rathke s pou and embraces the neural lobe anteriorly and laterally It loses its connect with the pharyngeal epithelium at an early stage.

The oral portion can be further divided into (1) the anterior lobe proper landular lobe, sometimes called the distal lobe (2) the pars intermedia (3) the pars tuberalis The pars intermedia borders on the neural lobe often contains the residual lumen of Rathke s pouch which is filled with lloid substance. In man, this part is vestigial. The pars tuberalis is an ision of the anterior lobe along the stalk and onto the tuber cinereum on loor of the third ventricle.

The anterior lobe of the pituitary gland is the site of production of nones which directly or indirectly influence the skeleton. The functional of the glandular part of the hypophysis are of three types (1) the chief , or chromophobe cells (2) the eosinophil, acidophil oxyphil or alpha, and (3) the basophil cyanophil or beta cells. The chief cells, said to eserve cells, are characterized by an agranular feebly staining cytoplasm two types of chromophil cells, that is, eosinophil and basophil cells, are to develop from the reserve cells by the elaboration of either acidophil or ophil granules.

Most authors ascribe to the pituitary gland the elaboration of six hor ies. Two of these seem to act directly on target organs, namely the wth promoting and the lactogenic hormones. The other hormones the two adotropic hormones, the thyrotropic and the adrenocorticotropic hormone, act irectly by stimulating other endocrine glands. Because of its influence on er endocrine glands the pituitary gland is often designated as the master nd of the animal body This relation between pituitary and other glands be understood as a feed back mechanism controlling and limiting the monal output of the peripheral endocrine glands. A comparison between parathyroid glands and, for instance the adrenal cortex shows the ferent mechanisms in the functional cycle of endocrine glands. The function the parathyroid gland is self limited. Functioning to maintain the physio- ic calcium blood level, the parathyroid glands are stimulated by a fall and ibited by a rise in the Ca ion concentration in the blood. On the other nd a similar automatism does not obtain in the activities of the adrenal rtex where therefore a governor is indispensable The stimulating ect of the adrenocorticotropic hormone of the pituitary gland activates cells of the adrenal cortex. Whenever the cortical hormones are pro- ced in excess, they themselves act in an inhibiting capacity on the pituitary ind, terminating the production of adrenocorticotropic hormone and thus ibiting indirectly the activity of the adrenal cortex. The same mechanism true for the thyroid gland and the gonads.

Of the hormones elaborated by the pituitary gland, only five are of mediate interest in this discussion

1 The growth promoting hormone growth hormone or somatotropic rmone

2 The two gonadotropic hormones.

3. The thyrotropic hormone

4 The adrenocorticotropic hormone *

Instead of tropic (turned toward) the term trophic (nutrient) is now frequently used.

The growth hormone acts to stimulate directly and the thyrotropic hormone indirectly skeletal growth. The final effect of the gonadotropic and adrenocorticotropic hormones is antagonistic inhibiting growth

While there is general agreement on the production of growth hormone by the eosinophil or alpha cells the site of elaboration of other hormones is still controversial Much evidence speaks for the assumption that one or both gonadotropic hormones are produced by the basophil or beta cells.

There is, as yet, no possibility of observing directly the function of the endocrine glands. Their normal activity must be determined by indirect methods that is, by experimental and clinical observation. Hormonal deficiency or hormonal excess is produced experimentally or is observed in the patient and its effects noted

Hyperpituitarism

An understanding of the influence of the hypophysis on growth can be gained by a study of clinical cases in which a tumor or hypertrophy of the eosinophil cells leads to overproduction of the pituitary growth hormone. In such cases, the growth potential of the body and its organs is increased and the consequence is a more or less proportionate or entirely disproportionate overgrowth. Whether the one or the other will result depends on the time of onset of the disease

Giantism or Gigantism.—If overproduction of the growth hormone occurs in childhood or at the time of adolescence therefore at a time when generalized growth of the individual is still proceeding an exaggeration in size of the genetically fixed pattern will follow primarily because all the structures which are necessary to normal growth are still present. Two of these structures merit special attention the epiphyseal plates and the sutures and synchondroses of the skull. Growth of the neurocranium the brain case, is dependent on the growth of the brain The brain does not undergo excessive growth in cases of pituitary tumor and, therefore, the neurocranium retains its normal size. This fact is of interest because it proves that the presence of the growth hormone alone is not sufficient to promote growth in all parts of the body That an enlargement of the brain is lacking is, in part, explained by the fact that the hypophysis has no or little influence on ectodermal structures and that nerve cells lose their ability to divide in early life

The lack of increased sutural and endochondral growth of the neurocranium may exert some restraining influence on the overgrowth of the upper face that is so intimately united with the cranial base However sutural growth of the maxillary complex of bones is increased to some extent. The growth of the mandible as an independent bone with a cartilaginous growth center is accelerated even beyond the general overgrowth of the face.

The epiphyseal plates, the main sites of longitudinal growth of the trunk and extremities, are stimulated to abnormal activity and remain active for a longer period of time For this reason in early development of eosinophilic

adenoma of the hypophysis, the height of the body increases far beyond the normal, and giants who may reach a height of seven eight, or even almost nine feet develop

The epiphyseal growth which is primarily growth of cartilage has been the center of the *attention of certain authors* who have concluded that the pituitary growth hormone influences cartilaginous growth exclusively This is



Fig. 129.—Preadolescent hyperpituitarism. Age of the patient at time of observation, thirty-six years. Giantism with superimposed acromegalic features. Height, eight feet, three inches. (After Cushing.)

certainly a mistaken point of view Simultaneously with exaggerated longitudinal growth in giantism, the skeleton shows exaggerated transverse growth of tubular bones and considerable thickening of the bones of the skull in addition to cartilaginous changes.

Although the proportions of the human body are not much distorted in cases of giantism an absolute maintenance of the normal proportions *is* impossible (Fig 129) This is due, in part to the fact that *some* parts *of* the body

complete their growth so soon after birth that even an early onset of the disease has no influence on them. The brain and other higher sense organs are in this category and a disproportion of skull and face is therefore bound to develop. Secondary to this lack of growth of the cranial skeleton which is only partly compensated for by thickening of the bones of the skull, a disharmony between the upper and the lower jaws may develop. The upper jaw or better, the upper facial skeleton is at least partly dependent for its growth on the growth of the cranial base to which it is attached whereas the mandible grows as an isolated bone by endochondral ossification at the condyle. Giants, therefore show a preponderance of growth in the facial skeleton and sometimes a massiveness and protrusion of the mandible. In the jaws, there is a marked *disproportion between the size of the crowns of the teeth and the size* of the jawbones. The teeth show no enlargement, partly because their size is determined very early and partly because the growth hormone does not seem to influence epithelial growth. The size of the roots of the teeth may be increased by an overgrowth of cementum. The disproportion between teeth and jaws in pituitary giantism is interesting as compared with the finding of large teeth in large jaws in extinct giant races of mankind.

Since some of the epiphyseal plates ossify soon after puberty, while others persist to the twentieth or twenty-second year of life, many other minor variations and disproportions of limbs and parts of limbs can be expected if the tumor develops during adolescence the years of epiphyseal closure.

Acromegaly.—In contrast to giantism or hyperpituitarism of adolescence, acromegaly or hyperpituitarism of the adult is characterized by the early development of striking disharmonies of the body. The hypersecretion of the pituitary growth hormone also acts in the adult as a powerful growth stimulant. In addition to the fact that many internal organs enlarge, the skeleton tries to respond to the stimulus, but the response is limited by the fact that the principal sites of longitudinal growth, the epiphyseal plates, have already disappeared.

The following changes are enumerated as the classical symptoms of acromegaly enlargement of the terminal (acral) parts of the body—nose, fingers, toes overdevelopment of the masticatory skeleton, with enormous and disproportionate growth of the mandible, which protrudes and in which the teeth may be widely spaced a massiveness of all bones of the skeleton, the long bones being considerably thickened and the bodies of the vertebrae enormously enlarged extreme thickening of the bones of the skull and overgrowth of the supra-orbital ridges overgrowth of the ribs which are not only much heavier than normal, but are also elongated in the bony and cartilaginous parts their curvature is relatively flattened, so that a bovine chest with greatly increased anteroposterior dimension results. The resumption of proliferation of the articular cartilages in the deep layers leads, on the one hand, to growth of the epiphyseal part of the tubular bones by endochondral ossification and, on the other hand, to degenerative arthritic changes.

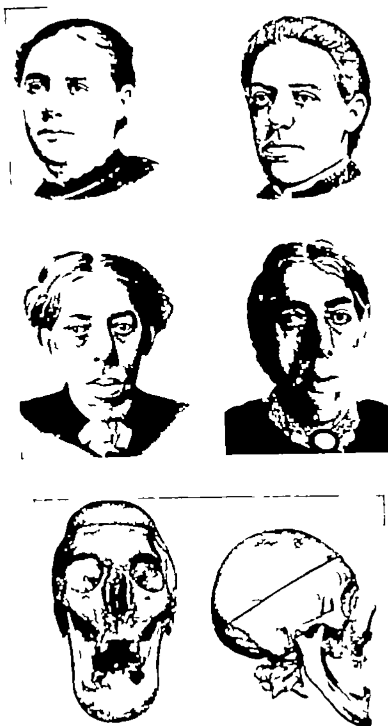


Fig. 130.—The typical facial changes in acromegaly. The four photographs show the patient at the ages of twenty-five, twenty-six, forty two, and forty three years, respectively. In the photographs of the skull, the mandible is in the position of greatest possible closure. Further movement was prevented by contact of coronoid process of the mandible with the maxillary tuber. For explanation, see text. (After Geddes.)

Some of the changes are easily understood as being a consequence of late hyperpituitarism leading to belated skeletal growth. Others must be discussed in detail. The enlargement of the nose is mainly due to the growth of its cartilaginous skeleton for example, septal cartilage, triangular cartilage and alar cartilages. The hypertrophy of the overlying subcutaneous and cutaneous tissues contributes to enlargement of the nose and is solely responsible for enlargement of the lips (Fig 130)

The elongation of the hands and feet is often first noted by the patient since he is forced to buy larger gloves and shoes. The hyperostosis of the terminal or nail phalanges, seen in roentgenograms as a tufting of the bones, does not seem fully to account for the elongation of the fingers. Probably the fact that each digit in the hand and foot consists of four segments (three in the thumb and in the big toe) is responsible for the considerable lengthening of the digits by small increments at the articular ends. Although increased endochondral ossification of the articular cartilages cannot contribute significantly to the length of the humerus, femur or similar long bones, an accumulation of small increments on seven sites on the three phalangeal digits will result in marked elongation The changes in the thorax may be explained by elongation of the ribs at the junction between bone and cartilage where a site of endochondral ossification persists. Since this is the only area where the ribs of an adult can grow the distortion of their shape and hence of the shape of the thorax, can be understood.

The growth of the vertebral bodies in acromegaly occurs almost exclusively by periosteal apposition of lamellated bone at the lateral and anterior surfaces of the body (Fig 131) This apposed bone is primarily compact bone. By resorption from within and replacement by spongy bone, a functional arrangement is again achieved. The intervertebral disc grows in transverse and anteroposterior diameter to the same extent as the vertebra itself The fibrocartilage differentiates, especially at the periphery of the disc and adjacent to the bone into hyaline cartilage. Thus, a new site for endochondral ossification is established, which creates a spur and a shelflike hyperostosis at the edges of the vertebral bodies.

The acromegalic changes in the skull though varying considerably in the different cases, show a distinct pattern The variations from this pattern depend, in part, on unknown conditions in part, on the sutural age of the individual at the time of onset of the disease. The sutures which play a determining role in the variations of the acromegalic skull are those of the facial skeleton.

Typical changes in the hyperpituitary skull observed on the skull of a forty three-year-old man with acromegaly (Figs. 132 to 138) will be described in greater detail for two reasons. First a detailed analysis of these changes has not been made before and second an analysis of this case furnishes many facts that are of importance for the understanding of the normal growth of the skull. The most conspicuous changes were an enormous growth of the cranial superstructures, namely the supra-orbital occipital and mastoid regions and

zygomatic arch an increase in facial height to which the maxilla and mandible contributed a nearly equal amount and a disproportionate overgrowth of the mandible in all dimensions. The brain capsule did not show changes other than those caused by the hypophyseal tumor and the increased intracranial pressure

In spite of the disharmonies between the upper and lower jaw and the reduction of functional masticatory stress to a minimum, all changes in the skull occurred as if in correlation with the overgrowth of the masticatory apparatus. In acromegaly the normal correlation of the cranial and the facial skeleton is changed in favor of the masticatory parts, resulting in a superficial resemblance to extinct races of mankind, a similarity which has often been noted. The development of the skull in the first years of life goes from a



Fig. 131.—The twelfth thoracic and third lumbar vertebrae seen from below. The acromegalic overgrowth of the bodies is clearly visible at their anterior and lateral surfaces. (After Erdheim.)

preponderance of the neurocranium to a gradual increase in the masticatory skeleton, and it is this period in which the cranial superstructures develop. The pathologic changes in the acromegalic skull can therefore also be seen as an exaggeration of these early growth changes to the point of the grotesque. It is characteristic of the development and growth of the cranial superstructures that they occur without participation of sutural growth by simple surface apposition of bone. For this reason, the hyperfunction of the hypophysis is capable of inducing their overgrowth even in an adult, when most of the sutures have already ceased growing.

The central feature of the acromegalic changes in the skull is the enormous enlargement of the mandible. The reason for the peculiar behavior of the

acromegalic mandible is to be found in its normal growth mechanism. The mandible grows by endochondral ossification at the condyle and by surface apposition in certain areas. The condylar growth increases the height of the ramus and over all length of the mandible Apposition at the alveolar crest serves to increase the height of the mandibular body There is, furthermore



Fig. 132.—Cranial base of the skull of a forty three-year-old man with acromegaly. Note the thickness of the bones, especially in the occipital region, the deeply excavated hypophyseal fossa, the projection of the supraorbital region, and the enormous size of the frontal sinus. (Specimen, courtesy the Department of Anatomy University of Chicago. Figs. 132 to 138 taken from the same specimen.)

apposition at the tip and posterior border of the coronoid process. Apposition at the posterior border of the ramus not only widens the ramus and lengthens the body but also determines the angle of the mandible. Molding apposition in the region of the chin continues, probably for a long time. Molding resorption acts especially on the anterior margin of condyloid and coronoid process and along the entire anterior border of the ramus.

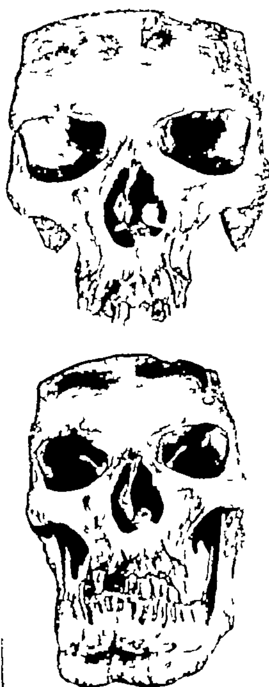


Fig 133.—Frontal views of the acromegalic skull.

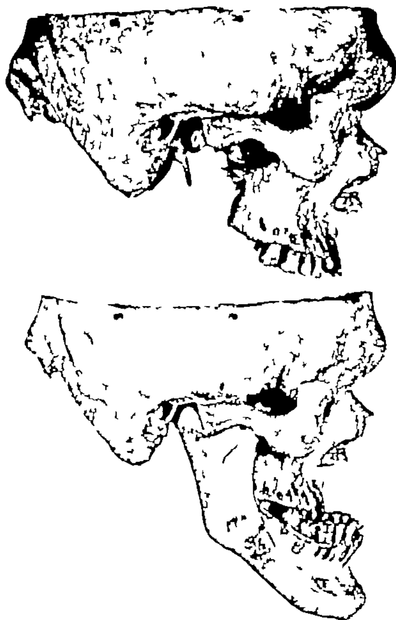


Fig. 134.—Right lateral views of the acromegalic skull.





Fig 136.—Left lateral views of the acromegalic skull.

In acromegaly, growth of the mandible can again be initiated and continued even at a time when growth has normally ceased because of the peculiar histologic structure of the condyle. Here, the bone in younger individuals is covered by a cap of hyaline cartilage which, in turn is covered by a thick layer of fibrous tissue Remnants of the hyaline cartilage which serves as a site of growth in the same way as the epiphyseal cartilage of long bones, persist even in old individuals. As long as this hyaline cartilage is present, its proliferation can again be set in motion by a hyperactive pituitary gland,

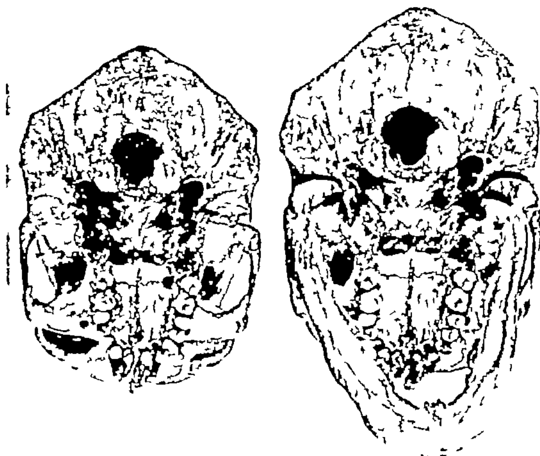


Fig 126—Basal view of the acromegalic skull.

and it will then assume its function as a growth center of the mandible where it left off at the termination of normal growth But even in cases in which an eosinophil adenoma of the hypophysis develops after the disappearance of the cartilaginous cap a differentiation of hyaline cartilage from the fibrous covering of the condyle is not only possible but also highly probable. If a new layer of hyaline cartilage has developed, endochondral growth can again set in after resorption of the terminal plate As in other bones, the periosteal appositional growth is stimulated by the growth hormone but this growth does not keep pace with the endochondral condylar growth and the effect is a gradual increase of the mandibular angle

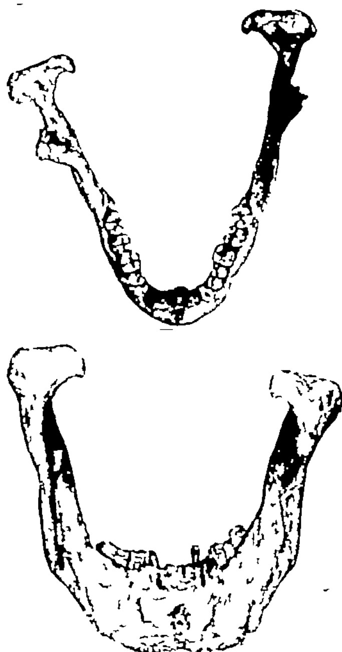


Fig. 117.—Superior and posterior iews of the cromegalic mandible.

The increase in over all length of the mandible and the increase in height of the ramus are inseparably linked with an increase in intercondylar distance, which is due to the divergence of the rami posteriorly The increase in height of the ramus causes as in normal development a separation of maxilla and mandible. The teeth erupt, and the alveolar process grows into the newly

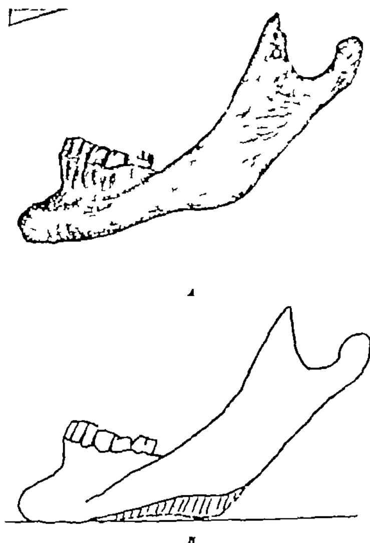


Fig. 128 —A Left lateral view of the acromegalic mandible. B Reconstruction of the area lost by resorption.

created space. This explains the increase in height of the bodies of the mandible and maxilla, an increase which results mainly from growth at the free borders of the alveolar processes. Thus, in fact, a new alveolar process develops in the upp and the lower jaw and, during this growth, the alveolar process gains a ain amount of independence from the maxillary and mandibular bodies. he mandible, this is expressed by the fact that the dental arch is not greatl larged despite the increase of the mandibular body The alveolar process ly widened in its distal parts by an accentuated diver

gence of the right and left molars. The teeth may remain in contact with each other or may be spaced. Spacing if present, is a secondary feature due to mechanical forces. By longitudinal growth of the mandible at the condyle, the alveolar process and the teeth are carried anteriorly so that the normal relation between upper and lower teeth is soon greatly disturbed The spacing of the lower teeth may then be due to the abnormal impact of the upper arch on the inner lingual surfaces and facets of the lower teeth This wedgelike action of the upper dental arch may be intensified by the pressure of the hypertrophied tongue (macroglossia) Extensive resorption of the roots of the upper and lower teeth can be regarded as proof of the mechanistic theory of spacing of the mandibular teeth in acromegaly The cementum hypertrophy observed on the proximal root surfaces is likewise caused by the intensified traction on the forcibly separated teeth

The alveolar process proper is united with the body of the mandible by a thin plate of bone which is thinnest in the anterior parts of the mandible (Fig 139) The formation of this bony plate replacing a rather massive part of the bone, doubtless results from the change in shape and functional stresses in the mandible the great increase in the height of the mandible measured between its lower border and the alveolar crest, and the decrease of forces acting upon the lower teeth especially the anterior teeth after disarticulation of the upper and lower dental arches. The independent growth of the functionless alveolar process leads to a more and more pronounced relative protrusion of the chin. This prominence of the bony chin is not only due to apposition of bone in the mental tuberosity but also to the posterior shift of the growing alveolar process.

The region of the mandibular angle deserves further attention. The lower border of the mandible about midway between gnathion and gonion, is bent so that it ascends rather steeply toward the region of the angle In addition, this part usually shows a marked concavity The deviation of the posterior part of the lower border of the mandible from the horizontal plane is caused without doubt, by far reaching resorption in this region. This can be recognized, for instance, by the relation of the mylohyoid line to the lower border of the mandible and by the fact that only a reconstruction of the resorbed parts can restore the length of the mandibular body and the height of the ramus to normal proportions. The reason for the secondary resorption in the area of insertion of the masseter and internal pterygoid muscles is obvious. The muscles of the adult seem to have lost the faculty of longitudinal growth. The condylar growth of the acromegalic mandible tends to increase the distance between the origin and the insertion of both masseter and internal pterygoid muscles. These muscles respond by increase of tone (stretching reflex) and the reaction of the bone to the increased traction is, interestingly enough resorption at the lower border of the mandible In the acromegalic skull examined this resorption was enough to keep the distance between the lower border of the zygomatic bone and mandibular angle normal although the total

height of the face had increased by about twenty five per cent. Photographs of other acromegalic skulls, for instance, the case of Geddes show identical changes in the region of the mandibular angle. The length of the temporal muscle is maintained by increased growth of the coronoid process.

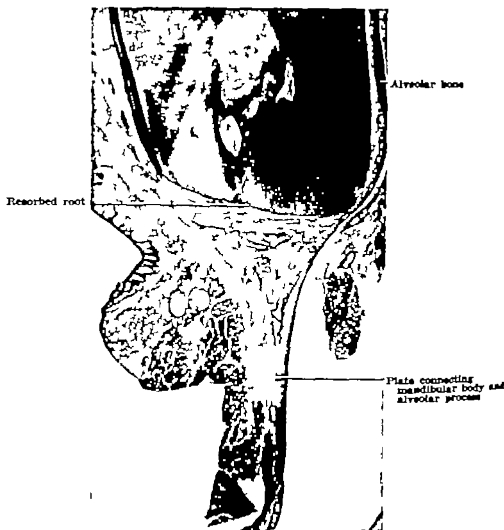


Fig. 119.—Labiolingual section through the lower right cuspid of a thirty-eight year-old man with acromegaly Note the extreme thinness of the bony plate connecting the body and alveolar process of the mandible. See diagram B

The areas of origin of the masticatory muscles are generally enlarged, and crests and irregularities are accentuated. This is true for the zygomatic arch, lateral plate of the pterygoid process, and infratemporal crest. The temporal line develops to a ɔad rounded bulge, which is especially high in its anterior and posterior par The area of origin of the temporal muscles is greatly widened and reac farther toward the midline than normally It should be noted that thes changes correspond to a hypertrophy of the masticatory

muscles that is an increase in functional cross section not an increase in length. The increase in volume of these muscles is explained by the over growth of the mandible.

It has been mentioned that continued growth of the mandible necessarily leads to an increase of intergonial and intercondylar distances, due to the divergence of the rami posteriorly Since the distance between the temporal articular surfaces cannot increase correspondingly adaptation of the temporal and mandibular components of the articulation has to be achieved by morphologic changes which involve both articulating bones. In the mandible the

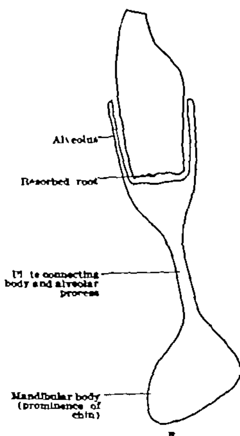


Fig. 119 —(*For complete legend see opposite page*)

condyle enlarges by apposition at its medial pole, so that, in spite of the increase of the intercondylar distance the distance between the medial condylar poles remains constant. The condyle itself is thus widened mediolaterally to about one and one-half the normal size. At the same time the temporal articular fossa and tubercle are extended laterally by appositional growth of the roots of the zygomatic processes. These changes are concomitant and coordinated with changes in the mastoid and tympanic region, which will be discussed later The result of the changes in the temporal bone is an extension of the articulating surfaces laterally to conform in width with the condyle

Restriction of movement in the joints seems to be quite marked and, as a consequence, the condyle and the neck are considerably flattened anteroposteriorly, especially on the right side.

The changes in the maxilla of the specimen described are entirely in accordance with the growth mechanism of the maxillary complex of bones which is, in many respects, entirely different from that of mandibular growth. In the maxilla, sutural growth plays the leading role in the transverse and anteroposterior plane. Sutural growth had evidently already ceased in the described case when the acromegalic changes were initiated. Therefore, the maxilla remained narrow and short and persisted in its normal relation to the cranial base. However the growth in height of the alveolar process occurs in the maxilla as in the mandible by apposition at the free borders of the alveolar crests. This vertical growth did occur and the maxilla is extremely high, the increase in height being confined to the subnasal region. The simultaneous apposition of bone in the alveolar fundi led to a coordinated overeruption of the teeth The functional dissociation of the alveolar process from the body of the maxilla finds its expression, first, in the extreme thinness of the basal parts of the alveolar process, which, in some places, is reduced to a translucent plate of bone resembling the comparable region in the mandible. The second relevant feature is the deep grooving of the maxillary body The grooves are extended onto the base of the alveolar process, forming deepened extensions of the canine and incisal fossa. Third, the pterygoid buttress of the maxillary complex did not grow vertically and its connection with the palatine and maxillary bone is now found an inch above the free border of the distal end of the alveolar process. This measurement permits an estimate of the vertical maxillary growth.

The growth of the mandible, as well as that of the maxilla, was definitely asymmetrical. The left condyle of the mandible grew more rapidly than the right and, as a consequence the midline of the mandible is shifted far toward the right, the left half of the mandible being longer and higher than the right. In the maxilla, the left alveolar process repeated this asymmetry by growing vertically downward, whereas the right alveolar process grew downward and *slightly outward. The asymmetry is still accentuated by* a lingual inclination of the left upper bicuspids and molars. As a consequence of this distortion in growth occlusal contact is found only between the left upper lateral incisor canine and premolars and the lingual cusps of the molars in the left mandible. Otherwise, the lower arch lies well outside the upper one. The right lateral teeth of the maxilla and mandible erupted beyond the occlusal plane so that from the right, the upper teeth seem to be almost entirely overlapped by the lower

At least three deviations from the described pattern which can be judged *typical for an adult with acromegaly have been observed* The disharmony between upper and lower jaw can be reduced either by inhibition of mandibular or increase in maxillary growth The latter is, in all probability possible only if facial sutures are still growing at the onset of the disease. A second varia

tion is due to the inhibition of vertical growth of the alveolar process, especially in the upper jaw as for instance in Geddes case (Fig 130) Because of lack of vertical growth of the alveolar process, the patient was unable to close her jaws. Third, a wide spacing of the lower teeth is often found. It is caused by mechanical factors during the unequal growth of upper and lower jaws (see page 223)

The changes in the supra-orbital region, characterized in the foregoing as the result of an exaggeration of normal growth consist in a marked forward bulging of the superciliary ridges. The bulging extends from one zygomatic process of the frontal bone to that of the other side. The zygomatic process itself juts outward. Only a shallow glabellar depression is present. The acromegalic supra-orbital torus is entirely different from that of extinct hominid races because it lacks a sharp superior boundary a fact which is correlated to the high development of the frontal lobe of the brain. The frontal sinuses have greatly expanded anteriorly laterally and superiorly Their enlargement is secondary to the growth of bone, as in normal development (see page 122)

As a counterpart of the supra-orbital torus, an occipital torus has developed, the superior nuchal line jutting out far posteriorly the external occipital protuberance is so prominent that the occipital bone at this point measures almost 40 millimeters in thickness. In accordance with this bony reinforcement, the entire vault of the skull is increased in thickness from four to five times. An inner and outer compact lamina are present but very thin in fact thinner than in most normal skulls. The diploë consists of dense, regularly arranged spongiosa.

The mastoid process is of surprising volume being enlarged in all three dimensions. Of great interest is the increase laterally by apposition on its external surface which is so pronounced that the greatest width of the skull is now found between the most prominent parts of the mastoid processes.

The lateral bulging of the mastoid region is coincident, and probably correlated, with the changes in the articular region of the temporal bone. It has been pointed out that the divergent growth of the mandibular rami necessitates a lateral expansion of the temporal articulating region, which comprises the articular fossa as well as the articular tubercle. The growth of the former is accompanied by lateral growth of the tympanic bone and of the posterior root of the zygomatic process. The expansion of the latter leads to an accentuated lateral projection of the transverse root of the zygomatic arch, and thus the zygomatic arch itself bends forward in a sharp angle.

Between the lateral projection of the transverse root at its posterior end and the lateral projection of the zygomatic process of the frontal bone at its anterior end, the whole zygomatic arch is shifted laterally to a sagittal position. This lateral shift of the zygomatic arches continued until they became visible in the norma verticalis of the skull. In this view they are obscured in a normal skull by the lateral convexity of the temporal region. The described changes of the zygomatic arch could not occur without cor

related changes in the malar bone and its anchorage to the maxillary bone. By these changes, the malar bone itself and the ascending frontosphenoidal process are turned so that they are in a sagittal plane.

All these changes lead to a considerable widening of the orbit laterally The separating wall between orbit and temporal groove is likewise greatly expanded but is thin and translucent.

The described changes of the skull can, in spite of many irregularities, still be classified under the law of functional adaptation The deviations from such a plan seem to be caused more by the inability of certain skeletal parts to grow proportionately to the others than by an irregular overgrowth of other regions. All this must be understood, of course, as falling within the limits of pathologic growth initiated by hyperpituitarism.

The enlargement of the supra-orbital and zygomatic regions is the direct result of hypertrophy of the masticatory apparatus, though the latter is, to a marked degree, limited to the mandible. Hypertrophy of the mastoid process, though partly due to expansion of the articulatory parts of the temporal bone, is mostly due to a change in the equilibrium of the head The enormous overgrowth of its anterior parts is offset by the hypertrophy of the balancing muscles, the sternocleidomastoids and the posterior muscles of the neck, which are responsible for the overgrowth of the mastoid process and the formation of the occipital torus

Hypopituitarism

Deficiency of the growth hormone is, in most cases caused by destruction of the anterior lobe of the hypophysis, brought about by the presence of extra hypophyseal tumors, for example, craniopharyngioma, by the development of cysts in the hypophysis, or by tuberculosis of the pituitary gland. In rare cases, there is an idiopathic deficiency of the eosinophil cells. Hyperpituitarism leads to proportionate or disproportionate overgrowth hypopituitarism, to the reverse—pituitary dwarfism or acromicria. Which clinical picture develops is dependent on the time of onset of the destructive or degenerative disease Hypopituitarism, at an early age, will lead to general cessation of growth, and fairly proportionate dwarfing of the whole body will result. If degeneration of the eosinophilic cells of the hypophysis occurs toward the end of the growth period, disharmonies will result because the acral parts of the body mainly the distal parts of the extremities, suffer more than the other parts. Thus the clinical picture of the acromicria develops.

Pituitary Dwarfism (Nanosomia Pituitaria) —The proportions of the skeleton of a pituitary dwarf are normal as far as they represent the proportions of an infantile skeleton prevailing at the time of onset of the disease (Fig 140) It is for this reason that the skull and the head are overly large. Eruption of teeth is always retarded. One of the most interesting features of hypopituitary dwarfism is the persistence of the epiphyseal plates and other synchondroses to old age. At first glance, this seems to contradict the fact that growth has entirely ceased, but this cessation of growth is of a quite different

order from cessation of normal growth. Normally proliferation of cartilage ceases, whereas its resorption by connective tissue elements and *its replacement* by bone proceeds until synostosis of the two bony elements (for example, the epiphysis and the diaphysis) is accomplished. In other words, although



Fig. 140.—Pituitary dwarf, *A*, thirteen years of age standing beside his brother *B* eight years of age. Note the short stature, rounded features, rather large head, prominent breasts, and underdeveloped sex organs. (After H. Seligman from W. Wolf.)

cartilaginous growth ceases, proliferation of connective tissue and growth of bone continues. In cases of pituitary deficiency growth of cartilage and growth of bone are arrested almost at the same time and the epiphyseal plates persist because growth has been interrupted, just as they persist in giantism, because growth is prolonged far beyond the normal time. The *only* change in the

region of the epiphyseal plate in pituitary dwarfism is the formation of a thin compact lamella of bone the terminal plate sealing the marrow spaces of the metaphysis against the cartilage (Fig. 141 *A*)



Fig. 141 —Costochondral junction of hypophysectomised rats.

A. A nimal twenty 6 days after hypophysectomy Arrest of endochondral growth and formation f t rminal plate

B Hypophysectomized animal, killed fter ten daily injections of growth hormone Terminal pl t has disappeared. Endochondral growth again active. (After R. D. Ray H M. Evans, and H. Becks courtesy Dr H. Becks.)

Acromicria.—The pathologic entity described as acromicria is, in its symptomatology and etiology the counterpart of acromegaly It has been observed only rarely and we know of only one case in which an autopsy has been performed. The skeletal features of the condition are general slenderness of the bones, with rarefaction of the compacta and spongiosa, smallness of the nose and facial skeleton, and shortness of the extremities, more marked in the distal than in the proximal parts. In the hypophysis of the one case which could be examined histologically the eosinophilic cells were almost entirely absent

Experimental hypophysectomy and experimental hyperpituitarism lead to changes in young animals which are comparable in all details to pituitary dwarfism and giantism in human pathology

Injections of the hypophyseal growth hormone into hypophysectomized rats lead to a reawakening of endochondral growth (Fig 141) These experiments provide a clue to the hyperpituitary changes in the adult (acromegaly)

THYROID GLAND

The thyroid gland which is situated laterally and in front of the larynx and upper trachea, develops from an epithelial budding on the floor of the primary oral cavity In the adult, its point of origin is still marked in the midline as the foramen cecum between the body and the base of the tongue The thyroid gland consists of spheric or ovoid follicles lined with simple cuboidal epithelium and filled with an eosinophil colloid. The shape of the epithelium and stainability of the colloid can be used as indicators of the functional status of the gland. Inactivity is indicated by a flattening of the epithelial cells and deeply staining colloid. Cuboidal or low columnar cells and lightly staining colloid are characteristic of a high degree of activity

The thyroid gland and hypophysis show an interesting interdependence. The hypophysis produces the thyrotropic hormone the presence of which is indispensable for the development growth, and activity of the thyroid gland. Excess of thyroid hormone inhibits the production of thyrotropic hormone by the pituitary gland and thus limits indirectly the activity of the thyroid gland. Lack of thyrotropic hormone explains the final involution of the thyroid gland after hypophysectomy The iodine-containing thyroid hormone itself is indispensable for the maintenance of the normal metabolic rate of the tissues.

Hypothyroidism

Hypothyroidism or aplasia of the thyroid gland and also experimental thyroidectomy or experimental destruction of the thyroid gland by certain drugs, for example thiouracil leads to a marked lowering of the rate of basal metabolism. The inhibiting effect of hypothyroidism on skeletal growth may be explained primarily by the inability of the target organ to react to the growth promoting hormone of the hypophysis. There is, however an additional factor The pituitary gland is of course influenced by the lowering of metabolic rate as any other organ. Specific changes in this gland after thyroidectomy have been described and consist of peculiar changes of the

basophil and eosinophil cells. The assumption, therefore, seems justified that hypothyroid dwarfism is the combined effect of damage to the target organ, the skeleton, and to the regulating endocrine gland, the hypophysis.

There seems, however to be an additional, more specific influence of the thyroid gland on the skeleton. Experimental injection of thyroxin into hypophysectomized and/or thyroidectomized rats shows in different bones different and still confusing results. However, it may be said that these experiments tend to prove an influence of the thyroid hormone on the *maturation of the skeleton* for instance, on the closure of the epiphyseal plates rather than on its growth.

Different types of thyroid dwarfism, as of pituitary dwarfism, are caused by differences in the time of onset of the primary disturbance. One can easily visualize a sequence of stages of hypothyroidism and hypopituitarism. The most severe changes are observed in cretinism, in which the thyroid gland is congenitally absent. Cretins attain a body height of from 70 to 100 centimeters.

Next follows the picture of infantile myxedema, in which degeneration of the thyroid gland occurs in early childhood. Those afflicted reach a height of from 100 to 150 centimeters. Then follows pituitary dwarfism, in which the effect of the destruction of the hypophysis becomes evident at puberty The height varies from 130 to 160 centimeters. The last and mildest type is acromicria, which occurs during the gradual termination of skeletal growth. Neither hypopituitarism nor hypothyroidism causes gross changes in the adult skeleton.

It must be emphasized once more that the analogy between pituitary and thyroid dwarfism holds true only for the skeleton and dentition. In other respects, hypopituitarism and hypothyroidism differ widely from each other Of the most striking differences, one is concerned with the mental ability which is unimpaired in the pituitary dwarf and greatly depressed in the thyroid dwarf. Another difference concerns the appearance The pituitary dwarf is generally normally proportioned the thyroid dwarf is often obese with a hard edema of the subcutaneous tissue (myxedema) (Fig 142) Hypogonadism is common to both pituitary and thyroid deficiency

The proportions of the skeleton and of the body of a cretin are those of an infant. The head is too large for the body and the cranial skeleton is relatively larger than the facial skeleton. The synchondroses at the cranial base and the sutures remain open. The teeth are retarded in development and in eruption but their size is not affected, and so the teeth and the alveolar process seem overly large for the body of the maxilla and mandible. The bodies of the vertebrae and therefore the vertebral column are short, and the intervertebral discs are sometimes as thick as the vertebral bodies themselves. The ribs are slender and in the sternum persistence of cartilage is characteristic. The limbs are short in proportion to trunk length, which again is characteristic for the infant body Epiphyseal cartilages and the cartilages in the cranial base persist when proliferation of cartilage has almost stopped, proliferation of the connective tissue in the adjacent marrow spaces also ceases. Apposition of bone probably in adaptation to functional stimuli produces, adjacent to the

cartilage a terminal plate sealing the marrow spaces of the epiphysis and the diaphysis. As is indicated by this description, the epiphyseal cartilage and the adjacent bone in the cretin appear identical to those in the pituitary dwarf. In addition to these changes parts of bones may remain cartilaginous

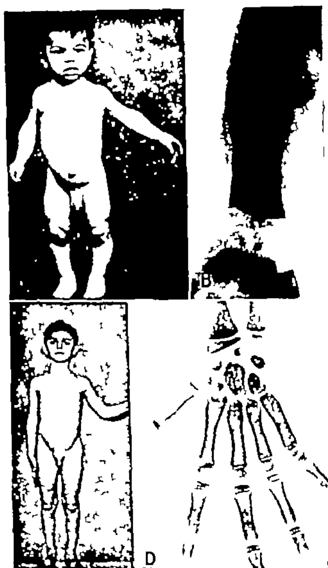


Fig. 142.—Hypothyroidism (After J Rosenblum from W Wolf.)

A and *B* Child six years of age. Note coarse features, stupid expression, protruding tongue, thick lips, and short extremities. Only one carpal bone ossified, corresponding to the age of two years.

C and *D* Same child two years after endocrine therapy

for a long time. In the scapula for instance the acromion, coracoid process, and vertebral border and in the clavicle both ends were found to consist of cartilage even in persons in their fifties.

In juvenile myxedema, the changes in the skeleton can be understood by visualizing an arrest of growth at an age somewhat greater than the critical

age in a cretin since, in these cases, hypothyroidism occurs between
and the twelfth years.

In hypothyroidism growth is not immediately arrested but g
tarded. The final phases of cartilaginous growth are further charact
an irregular arrangement of the multiplying chondrocytes These t
ties are visible as a fraying of the metaphyseal lines in a roentgeno
the epiphysis, the development of not one but several centers of calcific
ossification are also a characteristic feature of the roentgenogram
multiple centers of ossification fuse slowly to an irregular epiphy
(epiphyseal dysgenesis)

Absence or deficiency of the thyroid gland can be compensated fo
administration of dried thyroid gland or by the injection of thyro
success of this therapy depends to a large degree on its early initiation
this therapy children grow not only at a normal rate but someti
faster than normally until they attain fairly normal height. Myxedem
retardation and the depressed metabolic rate can be brought to n
nearly normal by administration of the thyroid hormone (Fig 142)

Hyperthyroidism

Hyperfunction of the thyroid gland (toxic goiter Graves disea
dow's disease) may lead in young individuals to acceleration of
growth In all probability this is caused primarily by the increased
olism and therefore reactivity of the entire organism and, second
the hyperfunction of the pituitary gland that participates in the
change

If the overproduction of thyroid hormone passes a certain lim
symptoms prevail. Toxic goiter of the adult may lead to simple oste
or mild osteitis fibrosa. In hyperthyroidism, enlargement of the par
gland has been found only in an insignificant number of cases and to
nificant degree in spite of careful examination. The mechanism of t
changes in hyperthyroidism is explained by the negative nitrogen bal
by direct influence of the thyroid hormone on the kidneys, increasing t
secretion of phosphates and calcium. The changes in the bones are the
to depletion of calcium and phosphorus. Reduced bone apposition and in
osteoclastic bone resorption in cases of toxic goiter are to be understood
tempt of the organism to mobilize enough calcium and phosphorus to com
for the increased loss of these elements.

MALE AND FEMALE SEX GLANDS

Testicles as well as ovaries function not only as organs producing
ex cells, but also as endocrine glands. In the male sex glands (teste
endocrine portion of the organ is represented by the interstitial cells of
They are large polyhedral epithelioid cells and are found in the con
tissue between the seminiferous tubules. The endocrine function of the

age in a cretin since, in these cases, hypothyroidism occurs between the sixth and the twelfth years.

In hypothyroidism, growth is not immediately arrested but greatly retarded. The final phases of cartilaginous growth are further characterized by an irregular arrangement of the multiplying chondrocytes. These irregularities are visible as a fraying of the metaphyseal lines in a roentgenogram. In the epiphysis, the development of not one but several centers of calcification and ossification are also a characteristic feature of the roentgenogram. These multiple centers of ossification fuse slowly to an irregular epiphyseal bone (epiphyseal dysgenesis).

Absence or deficiency of the thyroid gland can be compensated for by oral administration of dried thyroid gland or by the injection of thyroxin. The success of this therapy depends to a large degree on its early initiation. Under this therapy children grow not only at a normal rate but sometimes even faster than normally until they attain fairly normal height. Myxedema mental retardation, and the depressed metabolic rate can be brought to normal or *nearly normal by administration of the thyroid hormone (Fig. 142).*

Hyperthyroidism

Hyperfunction of the thyroid gland (toxic goiter Graves disease, Basedow's disease) may lead in young individuals to acceleration of skeletal growth In all probability this is caused primarily by the increased metabolism and therefore reactivity of the entire organism, and, secondarily by the hyperfunction of the pituitary gland that participates in the general change

If the overproduction of thyroid hormone passes a certain limit, toxic symptoms prevail. Toxic goiter of the adult may lead to simple osteoporosis or mild osteitis fibrosa. In hyperthyroidism, enlargement of the parathyroid gland has been found only in an insignificant number of cases and to an insignificant degree in spite of careful examination. The mechanism of the bone *changes in hyperthyroidism is explained by the negative nitrogen balance or* by direct influence of the thyroid hormone on the kidneys, increasing the renal secretion of phosphates and calcium. The changes in the bones are the response to depletion of calcium and phosphorus. Reduced bone apposition and increased osteoclastic bone resorption in cases of toxic goiter are to be understood as an attempt of the organism to mobilize enough calcium and phosphorus to compensate for the increased loss of these elements.

MALE AND FEMALE SEX GLANDS

Testicles as well as ovaries function not only as organs producing *mature* sex cells, but also as endocrine glands. In the male sex glands (testes) the endocrine portion of the organ is represented by the interstitial cells of Leydig. They are large polyhedral, epithelioid cells and are found in the connective tissue between the seminiferous tubules. The endocrine function of the ovary is performed mainly by the epithelial cells of the follicle. The sex hormone or

hormones of the male androgens, androsterone testosterone can easily be compared with the estrogens, the primary sex hormones of the female estrin or follicular hormone estrone estriol, estradiol

Sex hormones are produced in greater quantity at maturity a period in many animals coincident with the last sometimes accelerated, period of growth. The male sex hormones and the primary female sex hormone act finally as inhibitors upon the growth promoting function of the hypophysis. The hypophysis and gonads are interrelated in the following way The gonadotropic hormones of the hypophysis are indispensable for normal development and especially for maturation of the sex glands. Increase in the level of sex hormones leads to an inhibition of the secretion of gonadotropic hormones. In this way the pituitary gland acts to regulate the flow of sex hormones in a complicated feed back interaction In addition the sex hormones also seem to have an inhibitory influence on the elaboration of the growth hormone by the pituitary gland Thus sexual maturation initiates the termination of somatic growth

Gestation and placentation lead in mammals to the development of a secondary sex hormone corpus luteum hormone progesterone produced by the follicular cells after ovulation At this time the cells undergo rapid differentiation and, with the proliferating capsule theca of the follicle form the corpus luteum. The hormone of the corpus luteum produces the changes in the uterine mucosa which make implantation of the ovum possible and which finally culminate in the formation of the maternal placenta The corpus luteum hormone inhibits the growth and maturation of the ovarian follicles However the action of progesterone is possible only after the female organism is sensitized by the action of estrin

Hypogonadism

Some of the consequences of removal of the sex glands have been known for thousands of years and have been utilized by man all through history Castration of domestic animals, for instance, has been performed to change their behavior and their bodily development Castrated bulls can be used before the plough and give better meat. The results of castration in man were observed and portrayed by artists even in antiquity

The consequences of castration and of spaying were, for a long time, regarded as producing feminine characteristics in the male and masculine characteristics in the female. In reality after these operations, each sex approaches the neutral. In cattle, this type, in some characteristics, resembles rather closely the extinct species from which, in all probability the domesticated breeds of cattle originated. Only the changes in the skeleton can be discussed here. These can be reduced to a simple formula postponement of skeletal maturity and suppression of secondary sex characteristics. Epiphyseal cartilages especially continue proliferation beyond the time of normal closure The resultant overgrowth of the skeleton leads to a type of gigantism in which the extremities are long in comparison with the trunk (Fig 143) In

this connection, there should be mentioned the differences in body proportions which exist among human groups, in which maturity is normally reached at different ages. It is known that girls begin to menstruate earlier in an urban than in a rural population, and the latter show proportionately longer limbs than the former



Fig 143—Skeleton of an eunuchoid individual. Note the relative length of the extremities. Epiphyseal cartilages still present. (After Tandler and Gross.)

In the skull of castrated individuals the continuation of sutural growth is, as in other forms of giantism restricted to the facial skeleton, in which the mandible also grows beyond its allotted time There is no enlargement of the brain case since its growth is dependent on the enlargement of the brain. The result of this discrepancy between *facial and cranial* growth is a

certain prominence of the masticatory apparatus and an overdevelopm
the superciliary arches. The pelvis, after castration or spaying retains
fantile form which is characteristic for the period before the sex glands
maturity

The changes in the human skeleton described here are characteri
individuals who were castrated or who lost the sex glands by disease in
life and of those who suffer from a congenital hypogonadism. The findi
castrated or spayed animals confirm those observed in man.

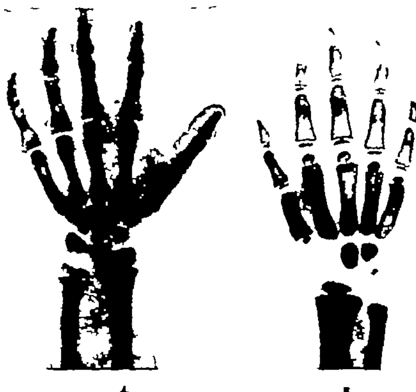


Fig. 144.—Hypergonadism. (After H. Zondek.)
A Roentgenogram of a hand of the three-year-old patient.
B Roentgenogram of a hand of a normal child three years of age.

Hypergonadism

Hypergonadism in man is restricted to precocious development of
glands. In animals, hypergonadism can be produced experimentally
injection of sex hormones. Precocious puberty is due to production of
hormone in the early months or years of life in a sufficient quantity t
maturation. It may be caused by a primary hypertrophy and hyperse
of the sex glands. In most cases, the overdevelopment of the testes or
is secondary to a tumor of the adrenal cortex. Tumors of the sex glan
also can cause hypergonadism.

Hypergonadism causes accelerated growth and maturation of the s
(Fig. 144) so that a child five years of age may attain a body he

140 centimeters. Roentgenograms may show that the ossification corresponds to the age of fifteen years. In spite of precocious and accelerated growth, these individuals remain rather small as a result of early maturity and, therefore, premature closure of the epiphyseal plates. This condition is in sharp contrast to hypopituitary and hypothyroid dwarfism, in which the epiphyseal cartilages persist to old age. The changes in growth in hypergonadism can be understood as somewhat distorted exaggeration of the normal pubertal spurt of growth which leads to termination of longitudinal growth.

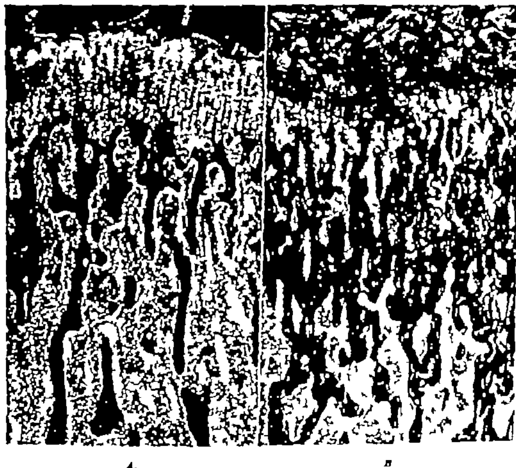


Fig. 144.—Proximal epiphyseal cartilage of the tibia of rats. (After M. E. Simpson, E. A. Kibrick, H. Becks, and H. M. Evans.)

A Normal animal.

B After six weekly subcutaneous implants of estradiol dipropionate, 10 mg. each, from the fifty fourth day. Animal killed at ninety-sixth day.

Note the restriction of cartilaginous proliferation and the osteosclerosis in the metaphysis.

Experimental Hypergonadism.—Injections of estrogen produce in normal female rats the following skeletal changes. The epiphyseal cartilages cease growing, the columnar arrangement of the cartilage cells becomes irregular, the rate of proliferation is diminished, calcification of the cartilaginous matrix is premature, bone is formed in the zone of calcification, and new bone rapidly fills up the medullary cavity and advances into the diaphyseal marrow cavity

by spreading over the inner surfaces of the cortex. Resorptive activity is not absent, but osteoblasts are predominant. There is no increased bone apposition at the periosteal surfaces (Figs. 145 and 146)

It may be noted that injections of estrogen in the rat do not cause epiphyseal closure in the tibia Here the termination of epiphyseal growth can be diagnosed histologically from the changes in the cartilage just described and from formation of a terminal bony plate sealing the marrow spaces in the metaphysis against the epiphyseal cartilage. The concomitant osteosclerosis of the metaphysis and neighboring parts of the diaphysis permit the histologic differentiation of hypergonadic and hypopituitary changes in this region.

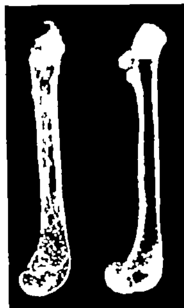


Fig. 146—Deposition of bone in the femur of a mouse after treatment with estrogen. Normal bone on right. (After W U Gardner and C. A. Pfeiffer)

Experimental findings in rats and mice and certain birds prove that injections of the female hormone act in a twofold manner On the one hand, they inhibit growth of the bones on the other side they cause hyperproduction of bone tissue. The sharp differentiation between the influence of the primary female sex hormone on bones and on bone tissue is important for realization that there is no basic difference between periosteum and endosteum as osteogenic tissues. That, after injections of estrogen, endosteal growth is stimulated, whereas no periosteal growth can be observed, can be explained as follows Apposition on the periosteal surface of a long bone is part of the growth of this element of the skeleton. Endosteal apposition leads to osteosclerosis. If skeletal growth is inhibited by the injection of estrogen, epiphyseal growth and growth at the articular cartilages cease, and thus longitudinal growth stops. At the same time, transverse growth comes to an end by cessation of apposition on the outer surface of the shaft. The endosteal

apposition, which is stimulated by the injection of estrogen, has nothing to do with skeletal growth. It is, instead, a means of storage of calcium and phosphorus by the organism. This storage, under the influence of the primary female sex hormones, can be regarded as an adaptation of the female organism to meet the needs, in recurrent periods, for great quantities of calcium or calcium and phosphorus in a short time As an example the adaptation of the skeleton of pigeons to the needs of the egg laying period may be quoted. These animals show an extensive osteosclerosis in the marrow cavity of the long bones during the period of maturation of the follicle During the formation and calcification of the eggshell this bone is rapidly resorbed by osteoclastic activity Hyperproduction of bone and elimination of the newly formed bone are repeated twice in short succession, corresponding to the production of two eggs during one mating period

It is important to consider the difference in mineral composition of bone and eggshell The main constituent of bone is calcium phosphate the main constituent of the eggshell, calcium carbonate. In the organism mobilization *of calcium is necessarily linked with mobilization of phosphorus. The surplus* phosphorus is eliminated during the time of bone destruction a possible association with a temporary parathyroid hyperactivity should be investigated.

Different species react differently to the injection of estrogen. In mice osteoblastic activity is intensified, while resorption of bone is depressed. In rats there seems to be only an inhibition of osteoclasis, while other species, for instance hamsters, guinea pigs, rabbits, dogs, and cats, are refractory to the application of estrogen The reason for this difference is not yet clear

Osteoporosis in older women has been explained as a consequence of lack of estrogens after menopause. Attempts at therapy by injection of sex hormones have not given uniform results.

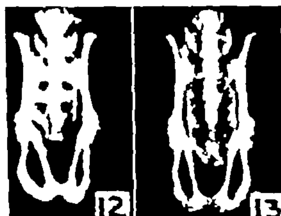
Secondary Female Sex Hormone (Progesterone)

The hormone of the corpus luteum, which is indispensable for normal gestation, is in many ways antagonistic to the primary hormone, the estrin. The antagonistic action is clearly visible in changes in the skeleton during pregnancy It has been maintained repeatedly that young women experience a spurt of growth during pregnancy This is possible, of course, only at a time when the epiphyseal cartilages are still present. After termination of generalized growth, skeletal changes which can be related to the action of the secondary female sex hormone are restricted to the pelvis. These changes are twofold enlargement of all diameters of the pelvic canal and relaxation of the pelvic ligaments. Growth of the pelvis in such cases occurs mostly at the symphysis, where simultaneous proliferation of the symphyseal cartilage and apposition of bone at the pubic bone are independent of the age of the individual. Additional growth occurs at the sacroiliac articulation, where the cartilages of the articulating surfaces of the sacrum and ileum may be the site of endochondral growth The phenomena of growth in the growing girl and in the mature woman are probably caused by elimination of the inhibiting action of estrin upon the hypophysis. This assumption that the changes described

may be hypophyseal is strengthened by the observation of development of "pregnancy cells" in the anterior lobe of the hypophysis. Though not identical with the eosinophilic cells, they are considered to be an intermediary form



A



B C

Fig. 147.—Sexual dimorphism and secondary pregnancy changes in the pelvis of a mouse. (After W. U. Gardner.)

A. Pelvis of an old male mouse (444 days). The pubic bones are well developed and converge medially.

B. Pelvis of primiparous mouse killed on day post partum. The pubic bones were separated by an interpubic ligament 2 millimeters long.

C. Pelvis of triparous mouse killed three days post partum at 431 days of age. At autopsy an interpubic ligament of 5 millimeters was observed. The pubic bones were thin and nearly parallel.

between chief cells and eosinophilic cells. Moreover, other changes occurring in the soft tissues of pregnant women, enlargement of the lips and a general coarsening of the features, are similar to acromegalic changes.

The increased mobility of the skeletal constituents of the *pelvis*, sacrum, and pelvic bones has been observed not only in the pregnant woman, but also

in certain animals for example, in the guinea pig and the mouse That the changes in the pubic ligament are dependent on the combined action of the follicular hormone and the hormone of the corpus luteum was assumed because in animal experiments injections of progestin produced relaxation and elongation of the pubic ligaments (Fig 147) There is, however considerable evidence that the effect of the female sex hormones is not direct but is mediated by a specific substance, relaxin. Relaxin is, in all probability produced by several parts of the female genital system, namely ovary uterus, and placenta.

PARATHYROID GLAND

The parathyroid glands which were discovered less than one hundred years ago are in man four small bodies lying on the posteromedial surface of the thyroid gland. The size of each gland is about 2 by 4 by 6 millimeters. The lower pair is slightly larger than the upper pair They are yellowish red, and it is by their color that they can best be differentiated from the thyroid gland. One or more of the glands may be embedded in the substance of the thyroid gland and so escape notice during operation or autopsy They develop from the third and fourth branchial pouch. During their development they shift in such a way that the third parathyroid becomes the lower gland, the fourth, the upper gland

The cells of the parathyroid gland are arranged in solid strands. Formation of irregular follicles occurs frequently The cells can be divided into two types The more numerous are the chief cells the less numerous, the eosinophilic or oxyphilic cells. As yet nothing is known about a special function of the oxyphilic cells, which appear only in the tenth year of life.

After injection of the parathyroid hormone (parathormone) the following changes occur

1 The excretion of phosphorus by the kidney is increased because of the inhibition of resorption of phosphorus from the tubules.
2. The calcium level in the blood rises.
3 Extensive osteoclastic resorption of bone begins soon after injection.

A correlation of these findings was attempted in different ways. The parathyroid hormone was said by some to increase primarily the power of the blood plasma to dissolve calcium. Others contended that the parathyroid hormone primarily stimulates the differentiation of osteoclasts and thus initiates resorption of bone A third explanation was that the primary effect is in the action upon the kidney Neither one of these assumptions can, by itself explain the variety of experimental and clinical findings.

The following working hypothesis is here suggested The function of the parathyroid is to maintain the optimum calcium blood level. This is done by mobilizing calcium from the skeleton. Since, in the living organism, extraction of calcium from the skeleton is impossible, the mobilization of calcium can be done only by resorption of bone. Thus, the parathyroid glands are responsible for the differentiation of osteoclasts and the ensuing resorption of bone It

has been assumed that parathyroid hormone primarily leads to a degeneration of osteocytes, which, in turn, leads to osteoclastic resorption. There is as yet, no convincing evidence for this theory During bone resorption, not only calcium but also phosphorus is mobilized. The unphysiologic rise of the phosphorus blood level is counteracted by the second function of the parathyroids, its direct influence on the kidney where reabsorption of phosphorus in the tubuli is inhibited, and therefore the excretion of phosphorus is increased.

The two functions of the parathyroid hormone, increase of bone resorption and increase of excretion of phosphorus, are inseparably linked. The fact that after the experimental injection of the parathormone, the rise in phosphorus excretion precedes by several hours the differentiation of osteoclasts is easily explained. The two actions of the parathyroids on bone and kidney are initiated simultaneously The effect on the bone needs time to develop because osteoclasts have to differentiate in order to become active. The effect on the kidney expressed in a functional change in the tubular cells, takes place almost immediately Observations in cases of hyperparathyroidism make it highly probable that the parathyroid hormone has still another function which aids also in maintaining the calcium blood level. The parathyroid hormone seems to inhibit the calcification of newly formed bone thus preventing precipitation of the calcium liberated through bone resorption. This action of the parathyroid hormone is antagonistic to the action of vitamin D which promotes calcification. The interaction of vitamin D and the parathyroid hormone, which influences calcium metabolism and therefore affects the skeleton, will be discussed later (see page 294)

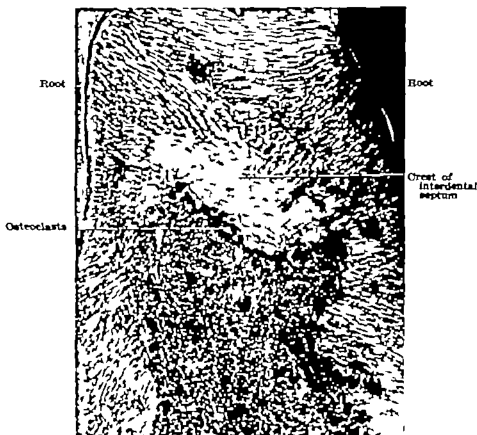
To summarize the working hypothesis regarding the parathyroid glands, it can be stated parathormone raises the calcium blood level by (1) causing osteoclastic resorption of bone (2) increasing excretion of phosphorus, and (3) inhibiting calcification of newly formed bone

Hyperparathyroidism

Experimentally hyperfunction of the parathyroid gland is simulated by the injection of parathyroid hormone. Clinically parathyroid hyperfunction is either primary that is caused by the presence of a tumor of the gland or secondary that is, caused by dietary deficiencies or renal changes.

A few minutes after injection of parathyroid hormone, the amount of phosphorus in the urine rises considerably Normally phosphorus is filtered in the glomerulus of the kidney but is, to a great extent reabsorbed in the convoluted tubuli. It is this reabsorption of phosphorus which is depressed or prevented by the overdose of parathormone In consequence of hyperexcretion of phosphorus, the phosphorus blood level decreases. Histologic examination of the bones of an animal twelve hours after injection shows a decrease in osteoblasts, a marked increase in the number of osteoclasts, and, as a consequence beginning osteoporosis. Simultaneously the bone marrow is replaced by young connective tissue including many giant cells, resulting in a fibrosis of the bone marrow (*Fig* 149)

The giant cells found in the tissue of the widened marrow spaces are, without doubt, osteoclasts which have survived the destruction of bone trabeculae. It is, in fact, in some instances possible to reconstruct the former outline of bone by the presence of giant cells in connective tissue (Fig 148) The persistence of osteoclasts after the destruction of bone is unknown under normal conditions. Giant cells may persist in hyperparathyroidism under the influence of the hormone.



A.

FIG 148.—Photomicrographs of decalcified mesiodistal sections of the interdental alveolar septum between first and second upper molars, showing the effect of large doses of parathyroid hormones on the alveolar bone of rats kept on a normal diet. (Original magnification ×170 reduced to ⅔.) (After J P Weinmann and L Schour)

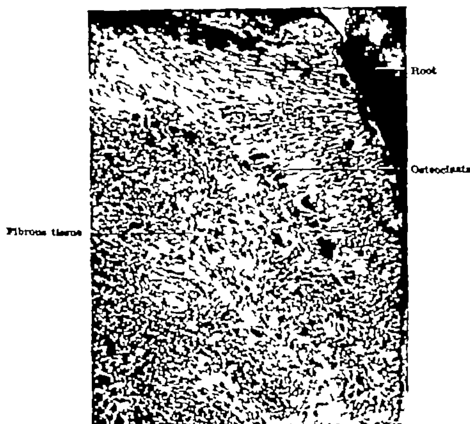
A After four injections of a total of 500 Hanson units. Alveolar bone resorbed except for a small cap of bone at the crest.

B After eight injections of a total of 900 Hanson units. Alveolar bone is entirely resorbed and replaced by fibrous tissue in which numerous osteoclasts persist.

After the onset of changes in the bone examination of the blood shows an increase in the calcium level. It is interesting to note that not all the bones or all parts of bone are affected to the same degree. The opinion seems justified that fast growing bones or fast growing areas of a bone are more severely affected This is easily understood if the fact is kept in mind that a higher rate of growth means not only more rapid apposition, but also a higher rate of reconstruction and, therefore more rapid resorption. The reaction of the

bone after injection of parathormone can therefore be described as an exaggeration of normal osteoclastic activity. It is well to mention at this point the fact that even the severest hyperparathyroidism does not cause resorption of teeth. With the exception of the period of shedding of the deciduous teeth, resorption is entirely absent in normal odontogenesis.

If injections of equally large doses of parathormone are repeated over a long period of time, the hormone gradually loses its effect. Later even complete healing of the primary damage is observed. The explanation for this puzzling fact has been sought in the elaboration of an antihormone in experimental animals which finally neutralizes the injected hormone.

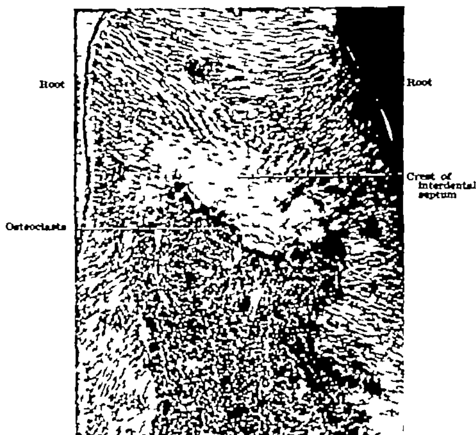


B

Fig. 148.—(For complete legend see opposite page.)

The formation of this antihormone may also explain the paradoxical findings after repeated injections of small doses of parathormone. Such experiments show that, after a brief period of increased osteoclastic activity, a reversal to increased osteoblastic activity takes place, resulting in osteosclerosis. If the injections are further continued, a normal balance of apposition and resorption of bone may finally be established. The hyperproduction of bone can be explained by the assumption that shortly after the first injections of small doses, the antihormone is produced in excess, neutralizing not only the

The giant cells found in the tissue of the widened marrow spaces are, without doubt, osteoclasts which have survived the destruction of bone trabeculae. It is, in fact, in some instances possible to reconstruct the former outline of bone by the presence of giant cells in connective tissue (Fig 148) The persistence of osteoclasts after the destruction of bone is unknown under normal conditions. Giant cells may persist in hyperparathyroidism under the influence of the hormone.



A

Fig 148 —Photomicrographs of decalcified mesiodistal sections of the interdental alveolar septum between first and second upper molars, showing the effect of large doses of parathyroid hormones on the alveolar bone of rats kept on a normal diet. (Original magnification X1 0 reduced to ½.) (After J P Weinmann and I. Schour)

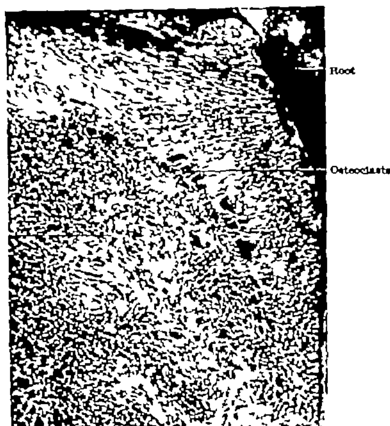
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injected hormone, but also part of the hormone produced by the glands of the experimental animal. In this way a secondary hypoparathyroidism results, *with consequent hyperproduction of bone.* Whether the injection of parathormone can lead also to a hypoplasia of the parathyroid glands (from inactivity) is not yet established. Such a hypoplasia could be a contributing factor in rendering repeated equal doses of parathyroid hormone less and less effective.



Fig. 149—Excessive deformities of the skeleton in osteitis fibrosa cystica generalisata (Recklinghausen's bone disease). Woman sixty-five years old. (After J. Erdheim from Haslhofer.)

Primary Hyperparathyroidism (Osteitis Fibrosa Cystica Generalisata) (Recklinghausen's Bone Disease).—Osteitis fibrosa cystica generalisata, a chronic and progressive disease, affects the entire skeleton. In advanced cases, we find a decreased strength of the bones which leads to deformities (Fig. 149). Spontaneous fractures occur frequently. The compact bone is replaced by spongy bone, the roentgenologic picture being one of generalized osteoporosis. The newly formed bone often remains uncalcified. In addition there is swelling of the bones from the presence of brown nodes or cysts. The marrow is changed into fibrous tissue in wide areas. The lungs, stomach, arteries, and most frequently the kidneys are the sites of multiple metastatic calcifications. In the kidneys they may lead to more or less severe damage with symptoms similar to those of Bright's disease. The enumerated skeletal symp-

toms of Recklinghausen's disease are not always developed to the same degree. The chemical examination of the blood shows an increase in calcium and phosphatase and a decrease in phosphorus. Calcium and phosphorus are increased in the urine. Tumors of one or more of the parathyroid glands are a regular finding.

The causal connection between tumors of the parathyroids and the bone changes of Recklinghausen's disease has been recognized only recently. For this reason many writers now prefer the term primary hyperparathyroidism to the older terms osteitis fibrosa or Recklinghausen's disease. That operative removal of the parathyroid tumors leads to healing (Fig. 150) is proof that the primary cause of the disturbances of the skeleton is, in fact, a hypersecretion of parathormone.



Fig. 150.—Healing of Recklinghausen's disease after removal of parathyroid tumor. (After J. Snapper.)
A. Left femur before operation.
B. Five years after operation.

Blood chemistry and urine chemistry in osteitis fibrosa cystica generalisata parallel the findings in experimental hyperparathyroidism. The same is true of the heightened activity of osteoclasts and of metastatic calcification. There are certain symptoms of clinical hyperparathyroidism which do not have a counterpart in experimentation. One difference is the finding of extensive

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A *B*

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Immature spongy bone

Cellular marrow

A.

Cyst

Spongy cortical layer

Cellular marrow

Cyst

B

Fig. 161 —A Cross section, and, B longitudinal section of humerus of a severe case of Recklinghausen's disease. Not the replacement of th cortical compacta by a wide layer of spongy bone in which numerous cysts developed. (Original magnification of A ×10, of B ×8; both reduced to ¾)

formation of new bone in osteitis fibrosa cystica generalisata. This difference can, in all probability, be explained by the factor of time. It is impossible to maintain hyperparathyroidism experimentally for any length of time comparable to the duration of clinical hyperparathyroidism in man. The newly formed bone is immature coarse-fibrillar spongy bone, which is characteristic of rapid



Fig. 152.—Longitudinal section through the ulna of the case shown in Fig. 151. Replacement of compact bone by irregular spongy bone. (Original magnification ×5, reduced to ⅘.)

bone formation. The matrix of this immature bone very often shows incomplete calcification, and parts of it remain uncalcified and persist for a long time as osteoid tissue. The failure of calcification can be explained by the assumption of an inhibiting action of the parathyroid hormone on vitamin D. The formation of new bone can be considered an inadequate attempt of the organism, in response to functional stimuli, to compensate for the loss of bone substance. In severe cases, the compact cortical bone may disappear entirely and it is then replaced by a thick layer of spongy bone (Figs. 151 and 152).

The trabeculae are extremely thin marrow spaces filled with fibrous tissue (Figs. 153 to 156) The original central marrow cavity is often considerably narrowed.

Another feature of osteitis fibrosa cystica generalisata which could not be duplicated in the experiment is the development of so-called giant-cell tumors or brown tumors, better termed brown nodes. These are observed in most cases of osteitis fibrosa cystica generalisata as multiple foci. Some of the nodes are later replaced by cysts, while others 'heal' by formation of new bone. *In all histologic details and in their possible fate, these foci are identical* with the solitary benign giant-cell nodes observed in patients who otherwise show no skeletal disease. It is possible that these two clinical types of giant-cell nodes are also pathogenetically more closely related than has been assumed This discussion must be postponed until secondary hyperparathyroidism and especially that of renal origin, has been described



Fig. 152.—From the patella of the case shown in Fig. 151 Newly formed and partly uncalcified bone trabeculae enclosing fibrous marrow Fatty and cellular marrow in adjacent marrow spaces. (Original magnification ×125 reduced to ⅔.)

The failure of the newly formed bone to calcify and the development of multiple metastatic calcifications seem to contradict each other The assumption that a specific action of the parathyroid hormone inhibits the calcifying action of vitamin D may shed light on this phenomenon. Calcification of osteoid tissue is bound up with local changes of the intercellular substance in which the osteoblasts *seem to have an active role* If these changes, normally stimulated by the action of vitamin D are inhibited, the osteoid tissue will persist The precipitation of calcium phosphates in other areas may be

caused by a combination of two factors increase of the calcium level in blood and in tissue fluid and the development of foci of necrosis caused by the toxic qualities of parathyroid hormone

Secondary Hyperparathyroidism.—Hypertrophy and therefore hypersecretion of the parathyroids has been observed under different experimental and clinical circumstances. Repeated injection of phosphates leads to one type of

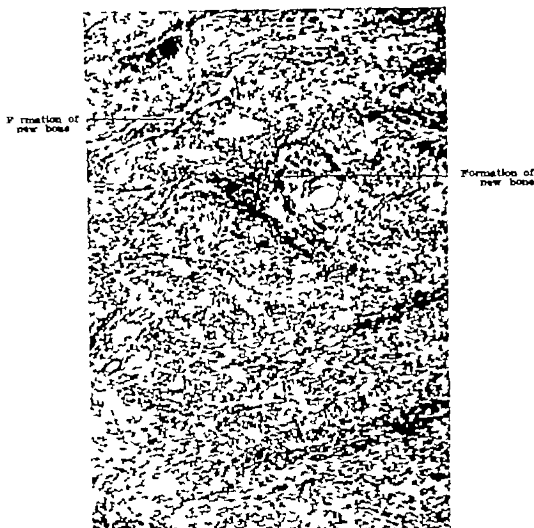


Fig 154.—Early stages of bone formation in the fibrous marrow Skull of the case shown in Fig. 151 (Original magnification X140 reduced to [illegible])

secondary hyperparathyroidism. The mechanism seems to be in accord with the action of the parathyroids upon the kidneys, which decreases reabsorption, and thus increases the excretion of phosphorus. This increased elimination of phosphates by a hyperactivity of the parathyroids is in direct response to the injection of phosphates.

Calcium deficiency too, is known to lead to secondary parathyroid hypertrophy The mechanism seems to be as *follows* The calcium blood level is

decreased and the organism attempts to restore this level by hyperactivity of the parathyroids and thus by mobilization of calcium from the skeleton. The final result of calcium deficiency will, therefore be either a generalized osteoporosis or osteomalacia if the destroyed bone is replaced by osteoid tissue. Calcium deficiency is rarely if ever caused by a lack of calcium in the diet. In most cases the deficiency is caused by a failure of the organism to absorb calcium. The absorption of calcium is linked with absorption of fat. If fat absorption is impaired by a lack of bile as in fistula of the common bile duct, or by disease of the intestinal tract itself as in celiac disease, a calcium deficiency will develop. The secondary hyperparathyroidism which can be observed in vitamin D deficiency will be discussed with this clinical picture.



Fig 155.—Numerous osteoclasts around newly formed and partly uncalcified bone trabeculae. Rib of case shown in Fig. 151. (Original magnification X125 reduced to ⅔.)

Other causes of hyperparathyroidism are certain chronic changes of the kidneys. At one time, the resulting changes in the skeleton were termed renal rickets. Today it is known that the renal disease causes changes in the skeleton which are identical to those of Recklinghausen's bone disease and that the variation in symptoms in different cases is mostly due to the grade of severity of the renal changes and to the age of the patient.

All pathologic changes in the kidney which lead to a reduction in functional renal tissue may cause a hypertrophy of the parathyroid glands. Such changes are congenital anomalies as seen in renal hypoplasia or polycystic kidney, chronic pyelonephritis, infection of the kidney and finally chronic

nephritis. A common symptom of all these diseases is the retention of phosphorus and therefore hyperphosphatemia This leads, as in experimental hyperphosphatemia to a hypertrophy of the parathyroids in an attempt of the organism to increase the excretion of phosphates. At the same time, the other actions of the enlarged parathyroids are necessarily set in motion that is, the increase in resorption of bone and the inhibition of calcification of bone and cartilage. The liberation of calcium and phosphorus will only tend to aggravate the condition Whatever the absolute values for blood phosphorus may be the calcium and phosphorus ratio is generally sharply unbalanced

The skeletal changes in renal hyperparathyroidism in adults are comparable with those of primary hyperparathyroidism or osteitis fibrosa cystica generalisata. In children, especially in the first years of life the changes in renal hyperparathyroidism are complicated because they involve a rapidly growing skeleton. The wide osteoid seams and the widened epiphyseal plates are so similar to those seen in rickets that this morbid entity has been called renal rickets. Though similar to rickets, these changes are of different etiology Whereas a primary deficiency of vitamin D is *the* factor in the development of rickets, the rachitoid changes in renal hyperparathyroidism are evidence of the inhibitory influence of hypertrophied parathyroids on the calcifying action of vitamin D Severe damage to the growing skeleton may result in dwarfism, for instance in Fanconi s syndrome

Latent Hyperparathyroidism.—Of great interest are localized and sometimes minute bone changes in cases of renal insufficiency Such changes have been observed in the vertebrae and more recently in the maxilla and mandible. In the latter cases, it could be shown that the localization of such foci of osteitis fibrosa is not haphazard. Instead, they occur in areas of the jaw which have suffered a mechanical or an infectious injury (Figs. 157 and 158) One of these lesions was found in the bony scar after extraction of a tooth. Others were in the neighborhood of infected roots. Another was in the neighborhood of an inflammatory polyp of the maxillary sinus. Such observations seem to indicate that moderate renal insufficiency may create a state of latent hyperparathyroidism, expressed in an increased lability of the skeleton The localized changes in such cases are the response of the sensitized skeleton to a localized injury Histologically we find the typical signs of osteitis fibrosa cystica localisata that is, increased resorption of bone formation of fibrous bone marrow and formation of immature bone which sometimes does not calcify In roentgenograms, such foci of osteitis fibrosa appear as defects of the bone because the immature bone is even if calcified, far more radiolucent than mature bone The difference in density is due to the fact that immature bone contains more cells and less intercellular substance and therefore also less calcium salts than mature bone.

Benign Giant-Cell Nodes and Bone Cysts.—Benign giant-cell nodes, or brown tumors, are found as multiple nodes in most cases of osteitis fibrosa cystica generalisata (Recklinghausen s bone disease) (Fig 159) Solitary nodes of the same histologic structure and of the same clinical behavior are found in

a seemingly normal skeleton (Fig 160) In the jaws, they occur either as cen l brown nodes (Fig 161) or as giant-cell epulis. Bone cysts which develop tly from brown tumors and partly independently are a frequent feature hyperparathyroidism (Fig 151 *B*) They are found as solitary cysts in the rmal skeleton.



A.

Fig. 156.—Different types of primitive bone in Recklinghausen bone disease Same case hown in Fig. 151.
A. Patella. (Original magnification ×125 reduced to ⅗)
B Skull. (Original magnification ×178 reduced to ⅗)

These giant-cell nodes (including the giant-cell epulis) are still a highly troversial subject. Three questions are still widely discussed. The first cerns the nature of these nodes, which are regarded as true tumors by some hors, whereas others look upon them as an excessive regenerative tissue wth. The second question is concerned with the identity of the brown es in Recklinghausen's disease, solitary brown nodes, and the giant-cell lis. The last and the more general question concerns the derivation and biologic significance of the giant cells in the nodes.

Histology of the Giant-Cell Nodes.—The giant-cell nodes consist of a stroma hin collagenous and mostly precollagenous or argyrophil fibers. The cells

are very numerous and most of them are round or spindle shaped and could be classified as young fibroblasts and undifferentiated mesenchymal cells, according to Maximow's terminology. The giant cells, multinucleated cells of varying size and shape, are found more or less evenly distributed in the node. Their number in a unit area is highly variable. Differences between these cells and osteoclasts are slight (Figs. 162 and 163). The localization of the nuclei in the center of the cell has been mentioned repeatedly as characteristic for the giant cells of the nodes. The changes in position of the



B

FIG. 164.—(For complete legend see opposite page.)

nuclei from an eccentric position in the osteoclasts to the center of the free giant cells is, in all probability, only a sign of the inactivity of the latter. Giant cells in brown nodes contain not infrequently phagocytosed erythrocytes.

Of great importance is the rich vascularization of the giant-cell nodes. The capillaries are especially wide, and the development of new capillaries by proliferation of the endothelium can be observed easily. Extravasation of red blood cells into the stroma is frequent and in a brown node, it is almost the rule to find areas of fresh hemorrhage or an accumulation of hemosiderin

pigment as a residue of previous bleeding. It is the frequency of these hemorrhages which is responsible for the reddish brown color of the nodes and for the widely used term brown tumors.

Brown nodes develop in the spongy bone of the epiphyses or in flat bones. Sometimes in hyperparathyroidism, they arise in the spongy bone which had replaced the cortical layer of a bone. Their growth inside a bone, of course, leads to destruction of bone. The reaction of the bone to the development of the brown node is characteristic. To compensate for the slow resorption of bone from within new bone is deposited on the periosteal or outer surface, so that for some time destruction of bone and formation of bone are almost balanced. This leads to a 'swelling' or 'thickening' of the involved bone, terms which should not be used without clearly stating the mechanism of the bone changes. The formation of new bone is seen by most authors as a walling



Fig. 157.—Roentgenogram of right and left lower molar region of a case of secondary hyperparathyroidism. Foci at mesial root of both third molars, *x* and *oo* and near the first molars, *o* and *xx*. (After J. P. Weinmann.)

in of the tumor or as a formation of a barrier against the progress of the tumor. This view is certainly erroneous. It stems from an analogy between a protective capsule of connective tissue and a bony shell. This analogy is not justified because connective tissue differentiates and condenses under the traction generated by expansive pressure, whereas bone is removed by resorption even under slight pressure if the force interferes with the circulation of blood in the bone. It seems to be much more in accordance with the biology of bone to view this phenomenon of formation of bone as a response to mechanical stimuli. It is the attempt of the organism to restore the strength of the involved bone which is weakened by the resorptive process. In extreme cases the bony shell may disappear in some areas of the node. A further growth of the node is then sometimes observed, being directed into the interstices between muscles, tendons, and ligaments but never infiltrating these organs.

A bony shell developing in the way just described is lacking only in one special type of giant-cell node, the giant-cell epulis. This growth originates in the bone of the alveolar process and is directed toward the surface. The



Fig 158.—A. Mesiodistal section through the left lower third molar Focus, eo in Fig. 157 indicated by broken line, consists of immature coarse fibrillar bone. (Original magnification ×5 reduced ½.)

B Detail of one of the foci. Primiti e bone trabeculae showing the interplay between bone esorption and bone apposition. (Original magnification ×150 reduced to ½.)

bone covering the primordium of a giant-cell epulis is so thin that the process of resorption leads to total destruction of the plate before there is time for any compensatory apposition on the outer surface



Fig. 159—Section through the parietal bone of the case shown in Fig. 151 Note the replacement of external and internal lamina and diploë by a network of primitive spongy bone. Bone development in a brown node. (Original magnification X8 reduced to ⅝)

Regenerative and Degenerative Changes of the Giant-Cell Nodes.—Healing of giant-cell nodes has been observed in cases of generalized osteitis fibrosa cystica generalisata (Recklinghausen's bone disease) after extirpation of the tumor or tumors of the parathyroids. Of greater interest are the numerous evidences of spontaneous healing of brown nodes. Healing can occur in nodes in osteitis fibrosa cystica generalisata in isolated nodes, and in giant-cell epulides.

The first phase of healing is a progressive fibrosis of the tissue of the node. During this process, the number of giant cells decreases to their final disappearance More and more collagenous fibers are seen in the tissue, the major

ity in all probability developing from the argyrophil precollagenous fibers. Concomitantly with the multiplication of fibers, the number of round and spindle cells decreases. Many of the capillaries seem to obliterate Grossly, the tumor is now firm and, on section pinkish white. This fibrosis seems to be a fairly common occurrence in the giant-cell epulis. Simultaneously with the fibrosis, or independently new formation of bone and, rarely of cartilage may occur in a brown node. Sometimes, these trabeculae of immature coarse

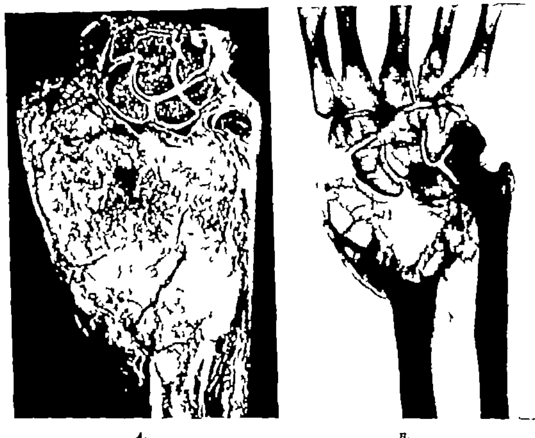


FIG. 160—Brown node (benign giant-cell node) of the distal end of the radius. (After L. Haslhofer)
A. Gross specimen.
B Roentgenogram.

fibrillar bone appear first in the periphery of the node. Sometimes they are laid down in strands of fibrous tissue which frequently separate the node into irregular lobules. The network of newly formed bone trabeculae may gradually spread throughout the entire node, replacing it, as it were, by spongy bone. The fibrous tissue between the trabeculae may even change to fatty or cellular marrow

The degenerative changes in giant-cell nodes are mainly three fatty degeneration of some elements and formation of pseudoxanthoma cells (foam cells) mucoid degeneration of the node, and, finally, formation of cysts. The foam cells seem to develop from phagocytic elements of the tissue of the node

which incorporate great numbers of fat droplets. They give the picture of foam cells if the fatty content is dissolved during histologic manipulation. The fatty content of the cells causes the yellowish hue of the tumor or parts of it.

Mucoid degeneration of tumor elements has been observed frequently. The most conspicuous degenerative change in a brown node is the development of one or more cysts in its tissue. *The origin of these cysts is probably* not identical in all cases. Some of these lesions arise from mucoid degenera-

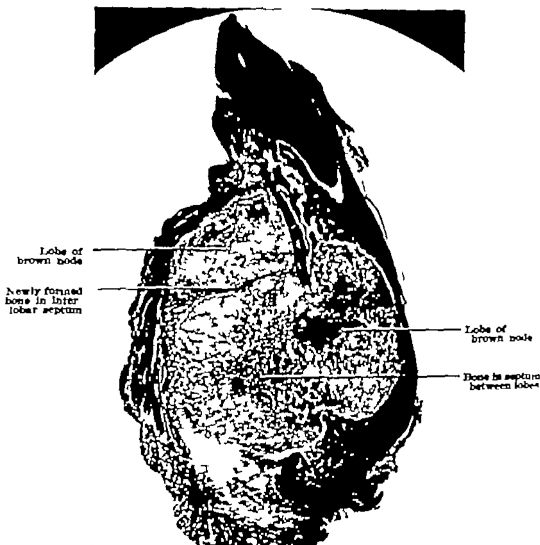


Fig. 161.—Brown node in the mandible. Note the formation of bone in the septa between lobes of the node. (After L. Haslhofer and W. Bauer, courtesy of Dr. Bauer.)

tion or liquefying necrosis of the tissue in the brown nodes. Others have their origin in extensive hemorrhage. Frequently more than one cyst can arise in one node. *The contents of a cyst are* either liquid or jellylike, colorless or yellow or brown. Sometimes fresh blood can be found in the cyst.

A study of the wall of a cyst shows that the cyst does not have a capsule of its own as long as it is situated in the tissue of a giant-cell node. The con-

tents of a cyst are in direct contact with the tissue elements of the node. The tissue in the immediate neighborhood of the cyst shows characteristically an edema, evident in irregular clefts between the cells. Some of the clefts communicate with the central space of the cyst, and thus some of the marginal cells are partly isolated and project into the cyst. After a time they assume a globular shape and, finally fully isolated, they drop into the fluid of the cyst where they liquefy (Figs. 164 and 165) The edema of the tissue surrounding the cyst can be interpreted as an infiltration of the tissue by the fluid of the cyst. It is by progressive erosion of the surrounding tissue that the cyst expands.

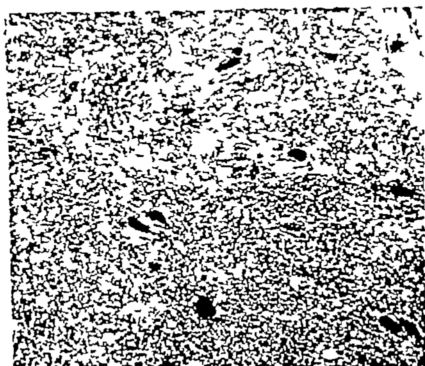


Fig 162.—Brown node from a rib of case shown in Fig 161 Note the numerous giant cells, the delicate, richly vascularized stroma, and the extensive fresh hemorrhages. (Original magnification X180; reduced t)

In many cysts, a great number of erythrocytes in varying states of disintegration can be found. We may deal in such cases with remnants of a hemorrhage which gave origin to a cyst or with the signs of a secondary hemorrhage into the cyst.

If the brown node has been entirely replaced by the cyst, the latter has a capsule of his own which consists of a rather thin layer of compressed connective tissue lining the cavity in the bone. Flattened fibroblasts on the inner surface of the capsule may imitate an endothelial lining

Bone cysts seem to expand by an increase of their fluid content and thus by increase of the pressure within the cyst a fact which can be recognized from progressive resorption of bone around the cyst. The increase of the contents is explained by an unavoidable disturbance of the circulation in the

immediate neighborhood of the primary cyst. Thus, a vicious circle is established the cyst causes stasis and diffusion of plasma or tissue fluid into its cavity whereby the cyst grows, and in growing it perpetuates the circulatory difficulties and thus its own growth. Spontaneous collapse and solidification of cysts seem to be rare.

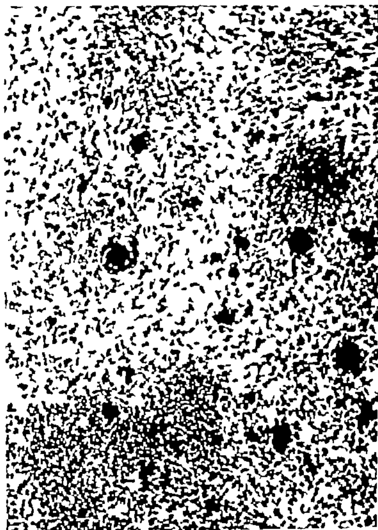


Fig. 163 —Giant-cell epulis. Note the different stages of development and degeneration of the giant cells and the multiple hemorrhages of different age. (Original magnification ×160 reduced to ⅘)

Cysts in persons affected by Recklinghausen's disease may develop primarily without previous development of a giant-cell node. The origin of such a cyst can, in most cases, be traced to hemorrhage in the bone. Liquefaction of the blood clot and progressive growth of the primary cyst can lead to the formation of large cavities in the involved bone.

The origin of the giant cells in brown nodes is still highly controversial. There is not only the more general question as to whether the giant cells differentiate from cells of the connective tissue or from endothelial cells, but also

the specific question as to whether these giant cells are osteoclasts persisting after the destruction of bone or whether they differentiate in the tissue of the node without relation to the bone.

As far as the origin of the osteoclasts is concerned, it can be stated that the evidence points more and more away from an endothelial differentiation of the osteoclastic giant cells. The second question can be answered only tentatively as long as the evidence is equivocal. Although rejected by some authors the assumption that the giant cells of the brown nodes are persisting osteoclasts

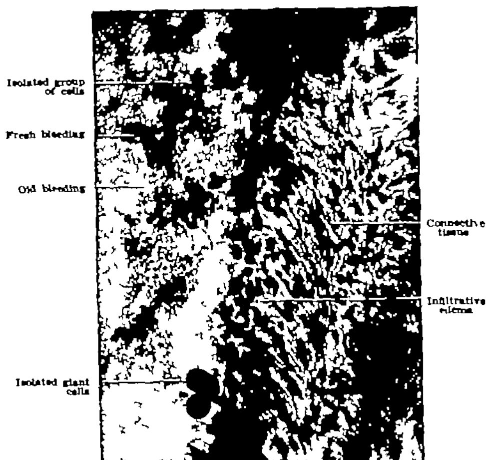


Fig. 164.—Cyst from the humerus of the case shown in Fig. 161. Contents with disintegrating and fresh erythrocytes. The cyst grows by infiltrating edema, isolating the elements of the brown node in which it developed.

still seems to be justified. The arguments against it point out mainly slight differences in shape, staining reaction, and position of the nuclei in the giant cells of brown nodes and osteoclasts. These differences could easily be explained by the fact that the typical osteoclasts are active bone-resorbing cells, whereas most giant cells in the node are in an inactive state.

The question must be answered as to whether it is probable that osteoclasts persist beyond the period of their resorptive activity. Normally osteoclasts disappear a short time after their task is completed. In fact they dis-

appear so quickly that it has been impossible to learn anything about the mode of their disappearance. The possibility of a survival of osteoclasts beyond their functional period is proved by observation in experimental hyper parathyroidism. In animals treated with large doses of the parathormone the destruction of bone by osteoclasis is, in some regions, very rapid. The osteoclasts which resorb this bone are seen to persist in the fibrous tissue which

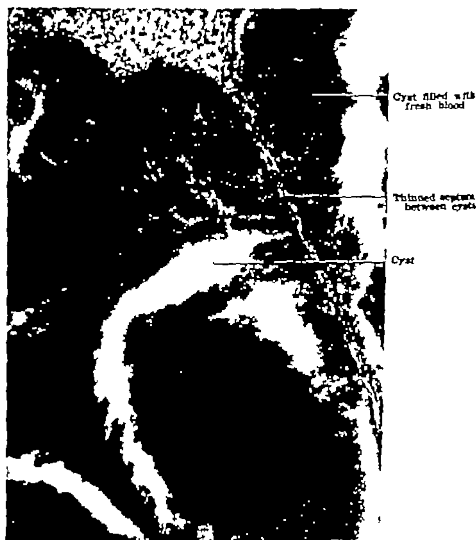


Fig 164.—Three cysts from the humerus f the case shown in Fig. 161 The cysts are separated by thin veil like plates of tissue. The degeneration of the septa will lead to the formation of a unilocular cyst. Contents of the cyst mostly blood.

replaces the bony trabeculae. One can even retrace the lost bone by follow ing the rows of osteoclasts (Fig. 148, *B*) That osteoclasts do persist in hyper parathyroidism does not seem strange if one recalls that the parathyroid hor mone is partly responsible for their differentiation. The influence of parathor mone on osteoclasts could be expressed by stating that the hormone causes differentiation of osteoclasts and a lengthening of their life span

The number of giant cells in a unit area of a brown node is, in most cases, not greater than that of active osteoclasts in a unit area of spongy bone In some areas of brown nodes, and especially in the giant-cell epulis, the presence of great clusters of giant cells cannot be explained by the persistence of osteoclasts only In the giant-cell epulis we deal in all probability with a differentia tion of new giant cells and not with a persistence of osteoclasts. This observa tion could be linked with the fact that this type of brown node is especially exposed to injuries and always shows large areas of hemorrhage Normally

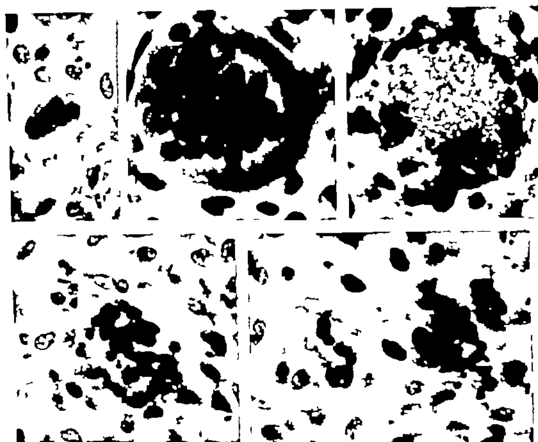


Fig. 166.—Differentiation and degeneration of giant cells from the epulis shown in Fig. 162. (Original magnification ×330; reduced to ⅔.)

it is the function of macrophages to remove blood pigment but it seems feasible that in hyperparathyroidism, the specific granulation tissue of a brown node tends to the differentiation of foreign body giant cells in reaction to the hemorrhage. Giant cells containing erythrocytes are in fact, found in giant-cell nodes.

In the epulis, the exaggerated reactions are responsible for the fact that here, better than in any other type of brown node, not only degeneration, but also differentiation of giant cells can be observed (Fig 166) Especially around areas of recent bleeding some of the round cells of the tissue assume greater proportions and the cytoplasm is more clearly visible and slightly acidophilic.

All stages, from these uninuclear foreign body cells to multinuclear giant cells, can be observed. Mitotic figures in these cells are rare, and it may be that the multiplication of the nuclei is by amitosis. *Degeneration of giant cells* is characterized by vacuolization of the cytoplasm, pyknosis of the nuclei, karyorrhexis, expulsion of nuclei, and, finally disintegration of the entire cell.

Another question with regard to the giant-cell nodes is that of the identity of these nodes in a skeleton affected with Recklinghausen's disease and an otherwise normal skeleton. In discussing secondary hyperparathyroidism, it has already been pointed out that observations of localized areas of osteitis fibrosa lead to the assumption of a state of latent hyperparathyroidism. In cases of moderate renal insufficiency the secondary hypertrophy of the parathyroids is not sufficient in itself to cause osteitis fibrosa cystica generalisata. Instead, it creates a state of latent lability of the skeleton, which then reacts in an exaggerated and specific way to injuries which would otherwise heal in an inconspicuous and normal manner The reaction itself is along the lines of osteitis fibrosa. A state of latent hyperparathyroidism, which is made probable by the observations quoted, can also be assumed hypothetically in individuals without renal disease. It could be compared with a state of latent hyperthyroidism which does not present any visible symptoms but which makes the *individual react more strongly to certain stimuli than a normal individual and* renders him highly susceptible to other noxae. The hypersensitivity of such persons to iodine is well known.

If the existence of latent hyperparathyroidism were accepted as a working hypothesis, the identity of the two clinical types of giant-cell nodes would be established. In both instances, the giant-cell node is the abnormal response of the skeleton to minor injuries under the influence of increased activity of the parathyroids. That trauma is an important factor if not the exclusive factor in the etiology of giant-cell nodes is assumed by all observers. Solitary giant-cell nodes are found in areas which are most commonly exposed to trauma the distal epiphysis of the femur the proximal epiphysis of the tibia, and the distal end of the radius.

The character of the giant-cell nodes is still under discussion. Most authors agree on the identification of the nodes in Recklinghausen's disease as *an excessive and somewhat aberrant granulation tissue. The* solitary giant cell nodes are still recognized by some authors as true blastomas and are frequently referred to as osteoclastomas, despite the well recognized fact that *they are histologically identical with the same structures in Recklinghausen's* disease.

Their often-observed spontaneous healing is also an argument against the classification of giant-cell nodes as true tumors. *If the pathogenesis of solitary* and multiple giant-cell nodes is determined on the basis of the hypothetical concept of latent hyperparathyroidism the solitary giant-cell nodes, as, for instance the giant-cell epulis, also have to be regarded *as excessive and somewhat* aberrant granulation tissue.

Solitary giant-cell nodes have long been regarded as tumors because of their slow but extensive growth, leading through compensatory *bone forma*

tion, to extensive "swelling" of the affected bone. Granted that there may be an intrinsic growth potential of the granulation tissue which simulates the independent and unlimited growth potential of a true tumor the reaction of the skeleton under an abnormal condition, that is, hyperparathyroidism should not be forgotten. Furthermore, the continued compensatory apposition of bone on the outer surface may to a marked degree, account for the continuation of resorption on the inner surface, and thus enlargement of the node. It is again the hyperparathyroidism which maintains this vicious circle.

Even those authors who reject identification of the giant-cell node as a blastoma continue to employ the term giant-cell tumor or brown tumor It is only logical to employ a new term to express the differentiation of the brown nodes from tumors, and the term used in the preceding pages, namely giant cell nodes or brown nodes, is suggested.



Fig. 147—Idiopathic hypoparathyroidism in fifteen-year-old boy. Note the advanced osteosclerosis. (After K. Emerson, F B. Walsh, and J E. Howard.)

Hypoparathyroidism

It is probable that hypoparathyroidism has an effect opposite to that of hyperparathyroidism. Bone resorption is decreased. The kidneys reabsorb more phosphorus than normally and the blood level of phosphorus rises. The organism disposes of the surplus phosphorus by combining it with calcium and depositing it in the form of newly produced bone or as meta

static calcifications. The calcium which is needed in this process of bone formation is taken from the blood. Thus, the calcium blood level falls below normal, and overexcitability of the nerve endings, chiefly the motor endings, results. In addition to the increase in bone apposition, bone resorption is greatly reduced. The combination of increased apposition and decreased resorption of bone may lead to progressive osteosclerosis (Fig 167)

In this connection, the much-discussed experiments of Erdheim, in which he produced rickets in rats by parathyroidectomy, should be mentioned. It has been pointed out repeatedly that Erdheim's rats were not fed a controlled diet. It is entirely justifiable to assume that the calcium intake of the animals was just high enough to assure normal ossification in the control animals. The increased apposition of bone after parathyroidectomy raised the calcium need above the available amount and as a consequence at least part of the bone formed in excess did not calcify. Thus the picture of rickets was simulated. In fact, in these experiments there is a combination of osteosclerosis and relative calcium deficiency. Misinterpretation of this experiment explains the repeated assertion that in rickets there is excessive formation of uncalcified or poorly calcified bone. In the chapter on rickets, it will be shown that this assertion is erroneous and that Erdheim's rats did not present a picture of genuine rickets.

In man, three types of hypoparathyroidism can be distinguished the postoperative, the neonatal, and the idiopathic type. The most striking manifestation of hypoparathyroidism is tetany caused by the deficiency of calcium in the serum. Calcium normally acts to diminish the irritability of the nerve endings. In rare cases in which the parathyroid glands are removed in a goiter operation the resultant hypoparathyroidism is fully analogous to experimental parathyroidectomy.

The second type is found in infants whose mothers had had a compensatory hyperparathyroidism during pregnancy caused, for example, by a primary or secondary calcium deficiency. In this case the fetus is provided with the necessary amount of calcium at the cost of the blood calcium of the mother and the maternal parathyroids hypertrophy to mobilize calcium from the skeleton. In consequence of the maternal hyperparathyroidism the fetus gets more parathyroid hormone directly from the mother than it would under normal circumstances and the development of its own parathyroids is arrested. Shortly after birth this lack of parathyroid function becomes manifest as tetany only to disappear again with the delayed but complete development of the parathyroids.

A third type is idiopathic hypoparathyroidism the cause of which is unknown. In rare cases of idiopathic hypoparathyroidism osteosclerosis can be ascertained roentgenographically (Fig 167)

CHAPTER VI

THE INFLUENCE OF VITAMINS ON BONE AND BONES

INTRODUCTION

To safeguard development, growth, and function of the body, the diet must contain, in addition to proteins, carbohydrates, fats, and minerals, elements which are called vitamins. These food elements, which are ingested in small quantities and are distributed by the blood stream to all the organs of the body, act in specific ways upon the different tissues. Their mode of action is similar to that of hormones and the analogy between vitamins and hormones has been stressed repeatedly. One could even speak of the product of endocrine glands as intrinsic hormones, of the vitamins, as extrinsic hormones. The former are elaborated in the animal body by specific organs, the latter are taken in with the diet as the finished or nearly finished product.

The terminology of the vitamins is still rather complicated and confusing. They were termed in the order of their discovery as A, B, C, etc. Later chemical names were introduced for some of them, and finally certain vitamins had to be subdivided after it became apparent that a single name had been given not to one but to a group of vitamins. Vitamin C, for instance, is ascorbic acid; vitamin B is broken up into B_1, B_2, etc., and each of these components has a chemical name also, for example, thiamin and riboflavin. In addition to these terms, terms which are derived from deficiency diseases are used. Since the lack of vitamin C causes scurvy or scorbutus, vitamin C is also known as the antiscorbutic vitamin.

Of all the vitamins, only A, B complex, C, and D will be discussed in this chapter since the influence of the other vitamins upon the skeleton has not been determined.

VITAMIN A

The fat-soluble vitamin A itself is contained in eggs milk, and liver Yellow and green vegetables contain carotene the provitamin A which is transformed to vitamin A in the body probably in the intestinal mucosa. Vitamin A is stored in great quantities in the liver A vitamin A deficiency can be produced not only by malnutrition (exogenous deficiency) but also by diseases of the intestinal tract (by lack of absorption) and of the liver (endogenous deficiency) Damage to the liver somehow prevents mobilization of vitamin A.

Avitaminosis A

Changes in the epithelium are the most characteristic symptoms of avitaminosis A. Highly differentiated epithelia are replaced by a keratinized squamous epithelium derived from the proliferating basal cell layer The epithelium thus changed is that of the salivary glands, the nasal cavity the trachea, the bronchi the genitourinary tract, the cornea, and the glands of the conjunctiva and lids.

Damage to the epithelial odontogenic organ of the continually growing rat incisor leads to an atrophy of the enamel forming cells and, therefore to enamel hypoplasias. In addition the inductive capacity of the odontogenic epithelium on the adjacent cells of the primary pulp is inhibited, and thus their differentiation into odontoblasts. This leads to changes in the dentin, occurring first in the dentin of the concave cementum-covered wall of the tooth. The convex, enamel-covered wall remains relatively unchanged for a time. In the end, there is abnormally thick dentin on the convex surface and abnormally thin dentin on the concave surfaces. *In complete vitamin A deficiency dentin formation may fail completely*

A further characteristic of vitamin A deficiency is night blindness, caused by the failure of the retina to produce rhodopsin (the visual purple)

While all authors agree on the characteristic changes in the epithelium, the findings regarding the skeleton are, in part, highly controversial. Endochondral bone growth is retarded and later ceases altogether The changes at the junction of the diaphysis and epiphysis or costochondral junction are not specific but are the general signs of interruption of longitudinal growth There is a shortening of the rows of cartilage cells and the bony trabeculae, denoting a decrease in proliferation of cartilage as well as in its resorption and replacement by bone. In the later stages, the cartilage cells lose their columnar arrangement and are found in irregular groups. At the epiphyseal end of the shaft a terminal plate develops. Periosteal apposition of bone continues for some time.

In experimental avitaminosis A, injections of alizarin red S have shown that the formation of new bone in the alveolar process of the white rat is

retarded and as a consequence, eruption of the teeth is delayed. In the dog retardation of bone growth leads to malposition of the teeth. The roots of the teeth of dogs deficient in vitamin A are malformed.

Marked neurologic changes which had been considered as a primary effect of vitamin A deficiency have been shown to be secondary to disturbances in growth of the cranial bones and the vertebrae.

The degeneration of nerves and the resultant paralysis are according to most observers, mechanically caused. There is a disproportion between the size of the brain and spinal cord, on the one hand, and the skull and vertebral column on the other The disproportionate size of the brain and spinal cord leads to herniation of parts of the brain and nerve roots and to damage by compression. The question which still needs clarification is whether the disproportion between brain and skull is caused by a cessation of skeletal growth while growth of the brain continues or whether there is an actual encroachment of the bones of the skull upon the brain space by overgrowth of the cranial bones.

It seems that sutural growth is inhibited and thus the main factor for enlargement of the cranial cavity is reduced or eliminated. It is of great interest that the tissue changes which contribute to the growth of bones suffer in order of their complication proliferation, degeneration, calcification, and resorption of cartilage cease first then proliferation of sutural connective tissue which alone permits sutural growth and last, the simple apposition of bone for example on periosteal surfaces.

The difficulties of an analysis of vitamin A deficiency are increased by damage to the kidneys. Calcification of the epithelium of the convoluted tubules and cloudy swelling of the cells of the collecting tubules were observed in addition to hornification of the pelvic epithelium. Such damage to the kid neys may cause symptoms of renal hyperparathyroidism that, in turn, may lead to osteoporosis sometimes observed in experimental vitamin A deficiency

Hypervitaminosis A

Investigations regarding the effect on the skeleton of experimental over dosage of vitamin A are still fragmentary There seems to be increased osteoclastic and reduced osteoblastic activity with some deficiency in calcification of osteoid tissue This may lead to osteoporosis or osteomalacia, with a marked tendency to fracture Examination of the teeth has shown little of histologic importance beyond a reduced rate of dentin formation. Extensive bone resorption in the absence of typical reparative processes was found in the supporting bone of the alveolar process in regions most subject to stress.

VITAMIN B COMPLEX

The most important vitamins making up the B complex are vitamin B_1 or thiamin, the beriberi preventing vitamin; vitamin B_2 or riboflavin; the nicotinic acid or pellagra preventing factor the filtrate factor which consists of pantothenic acid and other less known elements and B_{12} that plays an

important role in erythropoiesis. The B complex vitamins are contained in lean meat, especially pork and liver heart and other organs, in different vegetables, especially potatoes and carrots, and in rice polishings.

Experimental investigation of the influence of these vitamins on the skeleton is meager A deficiency of riboflavin in the diet of the pregnant female rat is responsible for congenital skeletal malformations in the offspring The results of these experiments seem to contradict the experience that the maternal store of vitamins 'either protect the offspring completely thus resulting in the delivery of normal young or in case of extreme dietary deficiency the embryos die in utero *Although there is some truth in this "all-or-none" theory it is not* entirely correct. Between the two extremes there exists a narrow range in which maternal nutritional deficiency may result in arrest of development of the embryo without causing death. In this case, congenital deformity of the offspring may be the result. '*

The malformations produced in these experiments consisted of shortening or absence of the tibia, fibula, radius, ulna and bones of the feet, shortening of the mandible and fusion of the ribs, with various deformities of the sternum maxilla, clavicle and scapula.

Histologic investigations reveal that the shortening of the long bones is visible in the cartilaginous stage and that ossification is retarded. Deformities of the cartilaginous model lead to abnormal shape and structure of the bone and to an abnormal course of the primary bone trabeculae.

Folic acid deficiency of pregnant rats causes similar defects and abnormalities in the offspring In addition it could be shown that deficiency restricted to some critical days during pregnancy will cause the most severe damage

In dogs, experiments were performed to investigate the consequences of the filtrate factor deficiency nicotinic acid deficiency and a deficiency of both *factors on the jaws. The results show that, in nicotinic acid deficiency* an inflammation of the gingival tissues develops. A filtrate deficiency leads, in the earlier stages, to hyperemia of the dental and paradental structures, followed by osteoporosis of the alveolar bone It is interesting that the alveolar bone proper is spared and osteoclastic destruction is limited to the supporting bone only It is furthermore of interest that the most extensive osteoporosis is found in the upper jaw The deficiency of both nicotinic acid and the filtrate factor leads to a combination of inflammatory and osteoporotic changes in the paradental structures.

VITAMIN C

The antiscorbutic vitamin C or ascorbic acid, is contained in highest concentration in citrus fruit green peppers, leafy vegetables, and walnuts before they ripen. It is possible to synthesize the pure ascorbic acid.

Warkany J and Schraffenberger E. Congenital Malformations Induced in Rats by Maternal Nutritional Deficiency VI. The Preventi e Factor J Nutrition 27 477 1944.

Deficiency of vitamin C presents a characteristic picture scurvy or scorbutus, which was one of the most dreaded dangers of long voyages on sailing ships, during the siege of towns, and on arctic and antarctic expeditions when people had to live on preserved or insufficient food for a long time. Today scurvy is still found in infants fed an artificial diet, in adults on an ill balanced diet, in persons suffering from alcoholism and in persons on a near starvation diet.

Scurvy is characterized clinically by the following symptoms extensive hemorrhages in the muscles of the extremities, especially the extensors, with resultant pseudoparalysis subperiosteal hemorrhages, especially in the vicinity of joints, add to the severe pain swelling and bleeding of the gums and loosening and loss of the teeth failure of wounds to heal. Children often assume a characteristic position in severe cases of scorbutus, with knees and hips slightly bent and abducted and rotated laterally Similar positions can sometimes be observed in the upper extremities. The position is assumed because of pain in the muscles and joints, which then are held in the position in which all or most of the parts of the capsule are relaxed (middle position) One characteristic symptom is observed in children only—epiphyseal separation, involving most commonly the lower epiphysis of the femur and tibia and the upper epiphysis of the humerus. It is, in all probability not spontaneous but is caused by slight trauma.

Three roentgenologic findings are characteristic (1) The shaft of the long bones has a ground-glass appearance due to osteoporosis (2) the zone of preparatory calcification of the epiphyseal cartilage is widened and becomes visible in the roentgenogram as an accentuated and broadened band (3) the region of the metaphysis bordering the epiphyseal line is a zone of rarefaction.

The histologic details of the changes in connective tissue cartilage, bone, and dentin as observed in experimental scurvy of guinea pigs can be summarized as follows Dentin formation is decreased and finally ceases altogether The layer of dentin formed during the initial stages of scurvy sometimes lacks dentinal tubules and has the appearance of an amorphous mass. The odontoblasts soon lose their characteristic columnar shape and their protoplasmic processes which normally fill the dentinal tubules. The odontoblasts seem to revert to a lower level of differentiation and show some morphologic characteristics of osteoblasts. They produce a bonelike tissue which more or less fills the pulp cavity The more acute the scurvy the smaller the amount of this hard tissue the damage to the odontoblasts seemingly being too extensive

The epidiaphyseal junction of the long bones or the costochondral junction of the ribs shows characteristic changes, indicating a decrease in the rate of growth as well as a qualitative defect of the formed cartilage and bone. The proliferation of cartilage is irregular (Figs. 168 to 174) The newly formed cartilage seems to contain less collagen than the normal. The preparatory calcification of cartilage is not impaired and the zone of calcification is widened. The apposition of bony trabeculae is greatly disturbed (Fig 173) In the early period of vitamin C deficiency the cells of the primary marrow produce a

rather homogeneous bonelike substance which is characterized by the lack of collagenous material and the presence of only a few cells. This bone of low differentiation and inferior quality may form considerable masses at the epiphyseal end of the metaphysis. The trabeculae of the adjacent parts of the shaft are thin and widely spaced. The compact bone often is replaced by spongiosa.

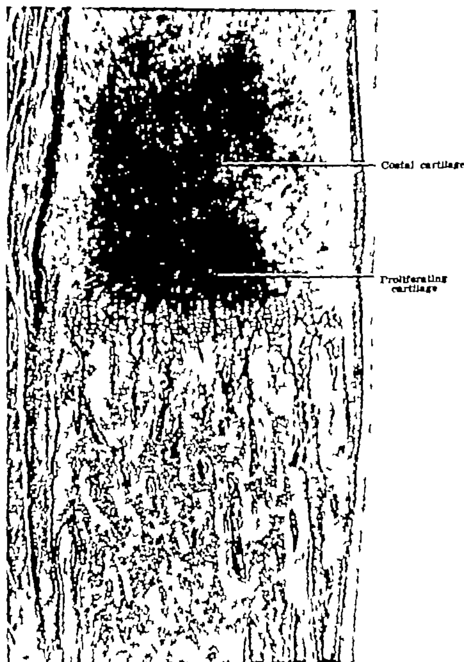


Fig. 168.—Costochondral junction of a normal young guinea pig. Note the disc-shaped proliferation zone of the cartilage, the zone of growth, and the zone of degenerative swelling of the chondrocytes. Regular arrangement of the columns. (Magnification X60.) (Specimen, courtesy Dr. F. Wassermann.)

The junction between bone and cartilage is weakened because of the osteoporosis on one side and the lack of interdigitation which normally develops between the regular spicules of cartilage and the trabeculae of bone. Fractures in this region of the ribs or at the junction of the diaphysis and epiphysis are therefore common (Figs. 172 and 174). The bone marrow near the cartilage may lose its cellular character, consisting mainly of a primitive type of connective tissue in



Fig. 169.—Detail of specimen shown in Fig. 168 in high magnification. Note the great width of the degenerated columnar zone of the cartilage. (Original magnification ×200 reduced to ⅘.)

which argyrophil fibers of precollagenous nature abound. The occurrence of the fibrous "Gerüstmark," framework marrow, is generally considered to be characteristic for scurvy. It seems probable that this change in the cellular marrow is secondary to fracture and greenstick fracture (Figs. 172 and 174).

Bone growth may cease altogether in later stages or in acute cases of scurvy. The cells of the periosteal cambium layer may then proliferate and form a rather thick layer not unlike a stratified epithelium. Compact bone



Fig. 176—Costochondral junction of guinea pig which was kept for four weeks on a vitamin C-deficient diet. Severe scurvy. Note th absence of a columnar layer of the cartilage and the scarcity of bone trabeculae. The cortical bone is thin. No sign of a fracture. The bone marrow abow severe hyperemia but remains ceflula (Magnification ×55.) (Specimen, courtesy Dr F Wassermann)

formed before the onset of the disease may gradually be replaced by spongy bone after resorption that starts in the marrow spaces. Differentiation of osteoclasts and their resorptive activity seem not to be influenced by vitamin C deficiency



FIG. 171.—Detail of section shown in Fig. 170 in high magnification. Note the irregular arrangement of the proliferating cartilage cells and the wavy border line of the cartilage. (Original magnification ×40, reduced to ½.)

Osteoblastic activity is at least greatly restricted so that in severe cases of experimental scurvy the amount of bone is considerably reduced. The weakened bone is rapidly reinforced by the production of a great amount of densely arranged spongy bone which develops on the periosteal surface of bones. This osteophytic bone is of the coarse fibrillar type.

The explanation of scorbutic osteoporosis as a result of restricted apposition and normal resorption is opposed by the theory that fibrous degeneration of the bone takes place in which the cementing substance and calcium salts disappear unmasking the fibrils. This breaking down of the bone, a process reversing that of bone *development*, is *said to occur without* osteo-

clastic activity Evidence of this type of degeneration of bone is, to say the least, inconclusive. Areas where great numbers of Sharpey's fibers are anchored to the bone are sometimes looked upon as foci of fibrous degeneration. Marrow spaces filled with fibrous marrow are sometimes said to be enlarged haversian canals in which between blood vessel and bone, a layer of fibrous tissue developed by disintegration of the haversian lamellae.

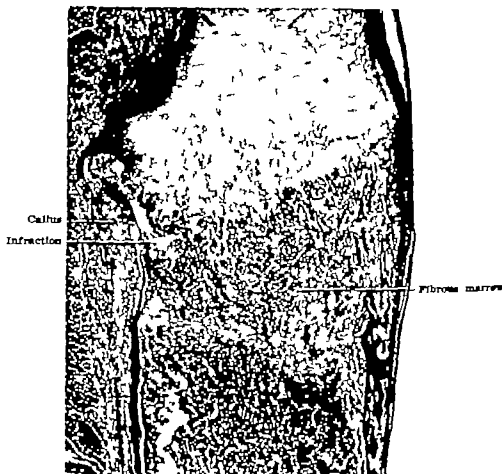


Fig. 172.—Costochondral junction of a guinea pig which was kept for four weeks on a vitamin C-deficient diet Severe scurvy *Note the calluslike proliferation of the cartilage* after an infraction at the costochondral junction. Severe osteoporosis. Replacement of the cellular marrow by fibrous marrow corresponding to the injured area. (Original magnification ×50 reduced to ¾.) (Specimen, courtesy Dr F Wassermann.)

The histopathology of bones in experimental scurvy shows striking and significant differences in young growing and adult animals. The latter show almost none of the characteristic symptoms seen in the young scorbutic animals osteoporosis, fractures, and fibrosis of the marrow These observations indicate that, at least for bone tissue, the disturbance of formation of new bone is much more important than the impairment of maintenance of the premorbid bone.

The loosening of the teeth so characteristic of human scurvy has also been observed in experiments. Histologically, the periodontium shows a typical

change. The well-organized principal fibers which function as a suspensory ligament of the tooth lose their functional arrangement and are replaced by loose connective tissue.

Most authors agree that vitamin C is necessary for normal formation and maintenance of the collagen fibers. The physicochemical changes in collagen formation are not yet fully understood and the theories regarding the mechanism of vitamin C deficiency are, therefore, hypothetical. It may be assumed



Fig. 173.—Detail of section shown in Fig. 172 in high magnification. Note the irregular arrangement of the cartilage cells and the almost total lack of bone formation. (Original magnification × 49 reduced to ⅔.)

that differentiation of the cells which are responsible for the elaboration of intercellular substances is impaired or even prevented. This seems to account for formation of bone in the pulp of teeth after formation of dentin has ceased. It is as if the cells of the connective tissue were no longer able to attain or to maintain the high level of differentiation of odontoblasts and so became active as osteoblasts. In other cases, the damage to the cells is so great that they revert to fibroblastic cells. Then any production of hard substance is interrupted. The osteoblasts at the epidiaphyseal junction may be either damaged

to such a degree that formation of new bone is impossible, or they might, in milder cases, produce a homogeneous matrix with but little collagen content.

Whether the teeth loosen solely from damage to the fibroblasts of the periodontal membrane or whether secondary inflammatory processes of the gingiva are largely responsible is not yet established. The disorganization of

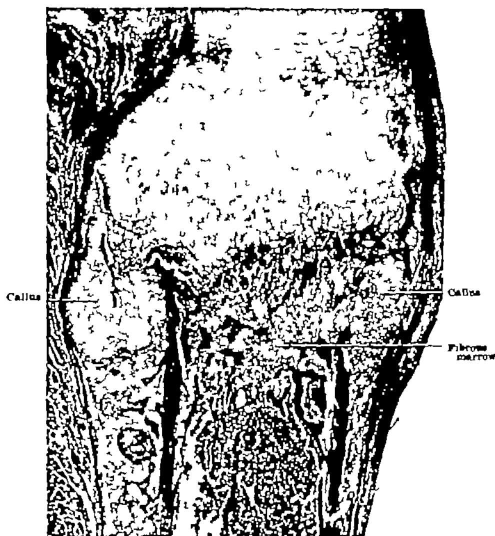


Fig 174—Costochondral junction of a guinea pig which was kept for four weeks on a vitamin C-deficient diet and had orange juice for six days before being sacrificed. Severe scurvy with first signs of repair Note extensive cartilaginous callus after a fracture. In the fibrous marrow and on the periosteal surface of the compacta, formation of primitive spongy bone Beginning rearrangement of the proliferating territories of the cartilage. (Original magnification ×60 reduced to ⅝) (Specimen, courtesy Dr F Wassermann.)

the principal fibers of the periodontal membrane can be explained by the fact that the continual eruptive and drifting movement of the teeth necessitate rather rapid replacement. A breakdown of the normal function of the fibroblast, with failure of collagen replacement, would lead to the picture described before

The gingival hemorrhages have been explained as being due to an increase in permeability of the capillary walls caused by deterioration of either the inter

cellular cementing substance or the connective tissue around the capillaries. The latter seems more probable The dense connective tissue of the gingiva normally protects the blood vessels. In the case of disorganization of connective tissue the capillaries in this region would be subjected to abnormal mechanical stress, which could easily explain the gingival bleeding the gingiva being normally exposed to buffeting and friction Similar changes might explain the intra muscular and subperiosteal hemorrhages all occurring in areas which normally are adapted to mechanical stress by specially organized connective tissue fascia of muscles, or Sharpey s fibers of the periosteum.

VITAMIN D

The ordinary mixed diet which is poor in vitamin D contains sufficient amounts of provitamin D ergosterol which changes into vitamin D on irradia tion with ultraviolet rays. The change of ergosterol to vitamin D occurs in the skin, where it is stored. Vitamin D can be obtained also by irradiation of food for example milk

The main sources of vitamin D are egg yolk and dairy products the main source of ergosterol is fats. The liver stores vitamin D to a different degree in different animals. Fish liver especially of the cod, the halibut and some sharks contains large amounts of vitamin D

Vitamin D deficiency is caused mainly by failure of the body to change ergosterol to vitamin D because of insufficient exposure to sunlight. The therapy therefore is irradiation with artificial or natural ultraviolet light or feeding of vitamin D in fish liver oil or irradiated ergosterol. Some patients seem to suffer from an acquired raised resistance to vitamin D (Milkman s syndrome) They develop all the signs of a severe osteomalacia often compli cated by pathologic fractures and react favorably only to heroic doses of vitamin D

Action of Vitamin D

The main function of vitamin D is regulation of the calcium phosphorus metabolism by maintaining the absolute level and the physiologic ratio of these two minerals. The mechanism of action of vitamin D has been worked out by numerous experiments. Any explanation of the action of vitamin D has to take into consideration the following facts which have been observed in clini cal and experimental vitamin D deficiency

1. The absorption of calcium, and secondarily of phosphorus, *from the* gastrointestinal tract is diminished.

2. The calcium blood level remains normal or nearly normal. The phosphorus level is depressed.

3 The excretion of phosphorus in the urine is increased.

4 The parathyroid glands are enlarged.

5 Calcification of cartilage osteoid and cementoid tissue and predentin is prevented

All these facts are explained by the assumption that vitamin D by direct action, furthers the absorption of calcium from the intestinal tract and, by

indirect action, the reabsorption of phosphorus in the kidney by depressing the function of the parathyroid glands. The effects of vitamin D deficiency can accordingly be analyzed in the following way The lowering of calcium absorption depresses secondarily the absorption of phosphorus because the calcium which remains in the lumen of the intestinal tract combines with the phosphorus to form insoluble calcium phosphate. The phosphorus deficiency

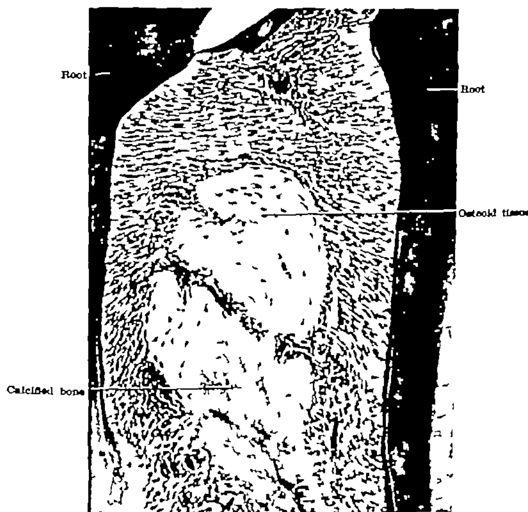


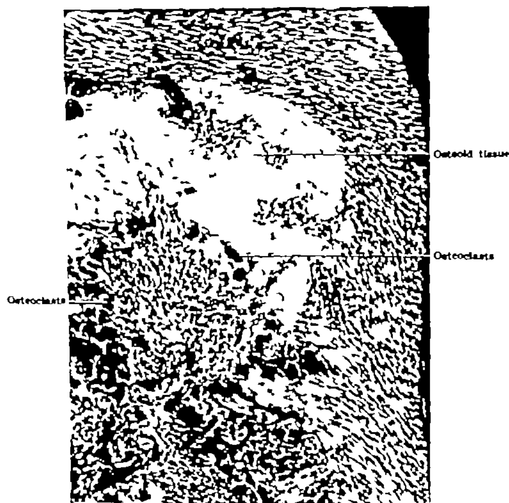
Fig. 175.—Experimental evidence for the resistance of osteoid tissue to resorption. (Original magnification ×170 reduced to ⅘.) (After J Weinmann and I. Schour.)

A. Crest of the alveolar septum between two molars of a rachitic rat. The entire crest consists of osteoid tissue. Calcified bone darkly stained.

B. Alveolar septum of a rachitic rat which was injected with 500 Hansen units of parathyroid hormone. Osteoclastic resorption of most of the calcified bone. Osteoid tissue remains intact.

is increased by the hyperactivity of the parathyroids, which are free of the inhibitory influence of vitamin D Under the influence of the hypersecretion and later of hypertrophy of the parathyroid, the reabsorption of phosphorus in the renal tubules is reduced in other words, the secretion of phosphorus in the urine is increased That the organism is depleted of phosphorus can be recognized by the fall of the phosphorus blood level

The calcium blood level in vitamin D deficiency remains fairly normal because almost all the calcium absorbed remains in the blood with failure of calcification of cartilage and osteoid tissue That vitamin D exerts a direct influence on the calcification of osteoid tissue and bone has been established Observations in cases of primary and secondary hyperparathyroidism suggest that this action may be hindered by overfunction of the parathyroids and that this phase of vitamin D activity is concerned with changes of osteoid tissue or the cartilaginous matrix which make these substances calcifiable

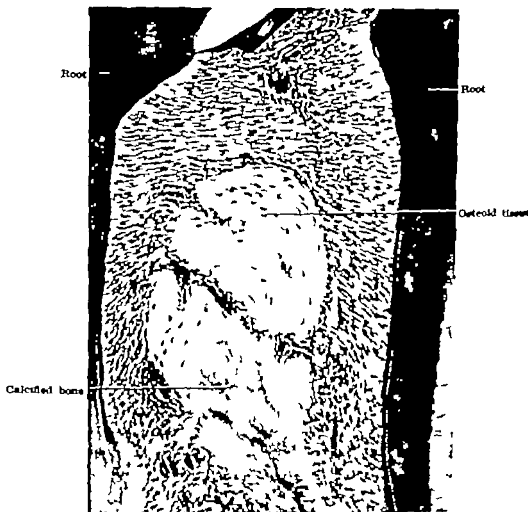


B

Fig 178.—(For complete legend see opposite page.)

The disturbance of calcification in vitamin D deficiency creates different pathologic pictures in different periods of life If the vitamin D deficiency occurs during the time of rapid growth, the pathologic changes will be greatest. The picture is then that of rickets. In the adult the consequences of vitamin D deficiency known as osteomalacia, will become manifest only after a long time

indirect action, the reabsorption of phosphorus in the kidney by depressing the function of the parathyroid glands. The effects of vitamin D deficiency can accordingly be analyzed in the following way The lowering of calcium absorption depresses secondarily the absorption of phosphorus because the calcium which remains in the lumen of the intestinal tract combines with the phosphorus to form insoluble calcium phosphate. The phosphorus deficiency



A.

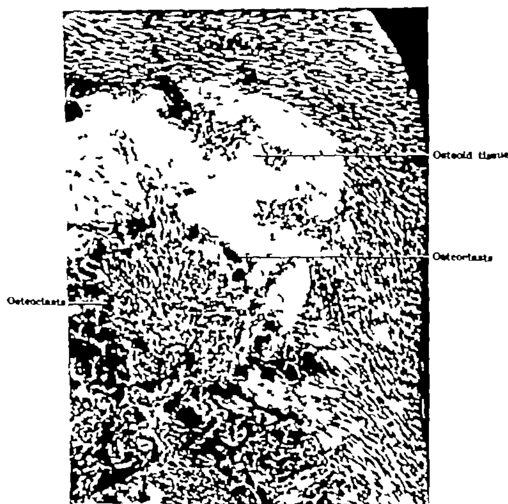
FIG. 175.—Experimental evidence for the resistance of osteoid tissue to resorption. (Original magnification ×1 0 reduced to ⅝) (After J Weinmann and I. Schour)

A. Crest of the alveolar septum between two molars of a rachitic rat. The entire crest consists of osteoid tissue. Calcified bone darkly stained.

B Alveolar septum of a rachitic rat which was injected with 800 Hansen units of parathyroid hormone. Osteoclastic resorption of most of th calcified bone. Osteoid tissue remains intact

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B

Fig 178.—(For complet[e] l[egend] see opposite page.)

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Vitamin D Deficiency

Rickets.—Rickets is a disease of early childhood with an onset mainly between the third and eighteenth months of life Newborn infants and those in the first month of life are rarely affected by vitamin D deficiency During fetal life, the minerals for the rapidly growing skeleton are provided by the mother Even if the mother suffers from a nutritional deficiency the fetus is, except in extreme cases, well protected, thriving at the expense of the mother During the years preceding puberty rickets is slightly more frequent than in the early years of childhood This vitamin D deficiency when manifest from the sixth to the fifteenth year of life, is known as late rickets

To understand the pathologic and clinical picture of rickets, it is necessary to differentiate between the effect of a vitamin D deficiency on bone and the effects of it on bones.

The first phase of the development of bone tissue that is, the formation of the organic matrix by the osteoblasts is undisturbed. The second phase, the mineralization of the matrix (calcification) does not take place, most probably because of the inhibition of the changes in the organic cementing substance that render it calcifiable The uncalcified osteoid tissue is highly resistant to osteoclastic resorption (Fig 175) and persists, therefore, in excessive amount, although formation of the bony intercellular substance is not increased. If vitamin D is added to the diet the transformation of osteoid tissue into calcified bone takes place in a surprisingly short time

The failure to calcify and the resultant resistance of the osteoid tissue to resorption lead to certain characteristic changes in the bones. Long bones grow in thickness at a normal rate by apposition on the periosteal surface The thickness of the cortical layer is increased and the marrow space narrowed. The thickening of the diaphyseal compact bone has been viewed as compensation for the mechanical insufficiency of the uncalcified bone. This view is not borne out by observation. Instead, one should regard the massiveness of the shaft as the inevitable result of lack of resorption.

Widening of the marrow space under normal conditions is, of course, caused by resorption of the cortical layer from within. This process of resorption should not be looked upon as a continual and uniform osteoclastic activity over the entire surface. As in most other areas, modeling and reconstructive resorption in many areas removes more of the bone than would be necessary for enlargement of the growing marrow space As a consequence, reparative and reconstructive apposition is always found on the inner surface of the cortical layer of long bones, alternating with areas of active resorption

In rickets, the resorption of the premorbid bone will continue in areas where resorption was active at the onset of the disease but will, *after a time*, be reversed in reparative apposition. Apposition will continue in those areas where it occurred in the first stages of the disease After a time all the surfaces of the premorbid bone will be covered by a layer of uncalcified osteoid tissue. When this happens, all resorption will cease and the cortical layer of the shaft will gradually increase in thickness, whereas the marrow cavity prevented from expansion, will remain narrow

Changes in the skull, often the first clinical manifestations of rickets, are especially marked, because the brain and skull show a greater rate of growth than any other part of the body in the first year of life that is, at the time of onset of the disease. In rickets, the greater the rate of growth, the greater the alterations in the bone

The enlargement of the brain capsule takes place by proliferation of cartilage at the cranial base and by proliferation of connective tissue in the sutures. However at least in one area namely at the temporal squama apposition on the outer surface and resorption on the inner surface contribute to the increase in the transverse diameter of the skull. In rickets the proliferation of cartilage is inhibited when the cartilaginous plates have reached a certain thickness without being replaced by bone. The lack of resorption in the temporal area and the lack of cartilaginous proliferation at the base may explain the accentuated compensatory growth of the sutural connective tissue at the cranial vault and therefore the persistence of fontanelles and the width of the sutures.

Modeling resorption plays also an important part in the necessary changes of curvature of the bones of the calvarium mainly frontal bones, parietal bones, and occipital squama. Resorption is confined to the marginal areas of the cerebral surfaces of these bony parts. The persistence of the prominent tubera of these bones in rickets, the bossing of the skull, is in all probability caused by the lack of this modeling resorption. In turn this deficiency may also somewhat contribute to the exaggerated sutural growth The prominence of the bosses gives the rachitic skull and head a peculiar angular appearance and also increases the circumference of the head. Thus the entire head appears too large and the change in the normal proportion is further increased by the underdevelopment of the rachitic body In the healing of rickets, the tubers may be flattened to a certain degree but often the bosses persist throughout life

In rachitic children, the bones at the lambdoid suture are often extremely thin. In areas of 2 to 4 centimeters, the skull can be dented with the finger This change of the skull is called craniotabes. Since it develops at the point where pressure is greatest in an infant which lies flat on its back it seems justifiable to think of the cause of this condition as mechanical. The pressure seems to diminish or to stop apposition of bone at the outer surface in this area while sutural growth continues. The theory of a mechanical etiology is supported by the observation that healing of craniotabes occurs even when the rachitic condition has not improved at the time the children begin to sit up and thus release the pressure in the occipital region.

In endochondral growth of bone the "provisional" calcification of the cartilage plays an important role. Only after calcification does the *orderly* resorption of cartilage take place In rickets, failure of calcification is not restricted to the bony matrix but involves *also* the matrix of hyaline cartilage (Fig 176) Replacement of the hyaline cartilage by bone is greatly disturbed and finally halted at the sites of endochondral growth of bone in the absence of calcification

Failure of the cartilage to calcify leads to severe disturbances. The cartilages which are sites of skeletal growth are the epiphyseal plates, which are responsible for the elongation of the shafts, the articular cartilages, which are responsible for the growth of the epiphysis the cartilages of the ribs, which, at the costochondral junctions, are mainly responsible for the longitudinal growth of the bony ribs, the cartilaginous models of the carpal and tarsal

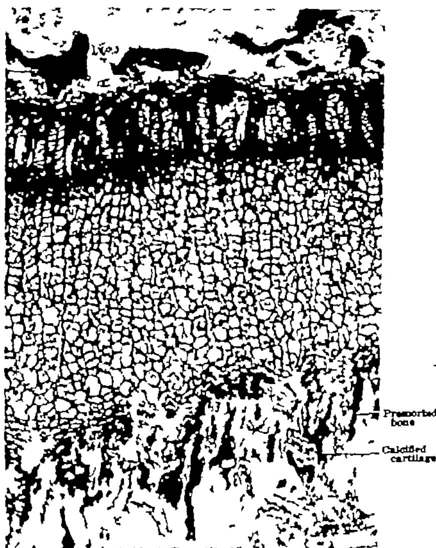


Fig. 174. —Undecalcified section of the epiphyseal plate of the tibia of a rachitic rat. Calcium-phosphatase stain after Gomori. Calcified tissue stained black. Note the calcified premorbid bone trabeculae in the epiphysis, the lack of calcification in the thickened epiphyseal cartilage, and the calcified premorbid cartilage which persists in the core of metaphyseal bone trabeculae. (Original magnification ×145 reduced to ⅝.) (Courtesy G. Gomori.)

bones and of the vertebral bodies the cartilages in the spheno-occipital and the intra-occipital synchondroses, which are responsible for the anteroposterior growth of the base of the skull and, finally the secondary hyaline cartilage of the mandibular condyle, which is responsible for the increase in height of the mandibular ramus and for the increase in over all length of the lower jaw

As a consequence of the inability of the cartilage to calcify the growth centers of cartilage bones and that of the mandible show a uniform and characteristic picture The calcification of cartilage does not cease abruptly the first sign that it has ceased being the irregularity of the zone of provisional calcification, which, in microscopic sections, normally appears as a narrow band. As a consequence of failure of calcification, resorption of the cartilage is not only retarded, but also irregular The blood vessels, which normally form regular loops penetrating the longitudinal columns of proliferating

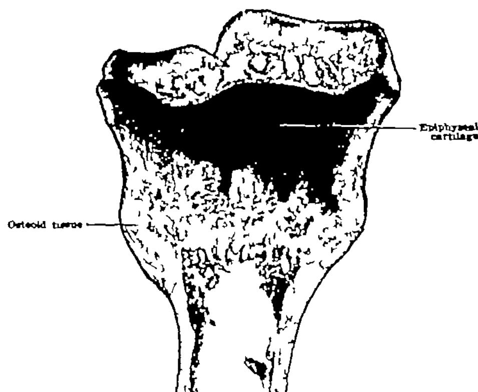


Fig. 177—Proximal end of the tibia of a rachitic rat. Note the clublike thickening of the metaphysis and the widening and irregularity of the epiphyseal plate. (Original magnification X18 reduced to ⅘.)

chondrocytes, instead form brushlike structures penetrating the cartilages in all directions. The proliferation of the cartilage proceeds for a time (Fig 178) but soon the proliferating cells no longer arrange themselves in the characteristic columns, forming instead irregular groups (Fig 177) Finally proliferation becomes slower and may even cease. However since proliferation of the cartilage continues far beyond the time when its resorption and replacement by bone stopped, the thickness of the cartilaginous plates is always greatly increased (Fig 177) This increase in thickness of the epiphyseal plates which is plainly visible in roentgenograms, is one of the clinical signs of rickets.

In rachitic animals that have survived the disease for a long time a resumption of resorption of the uncalcified cartilage and its replacement by osteoid tissue have been claimed. However one deals here not with resorp-



A.

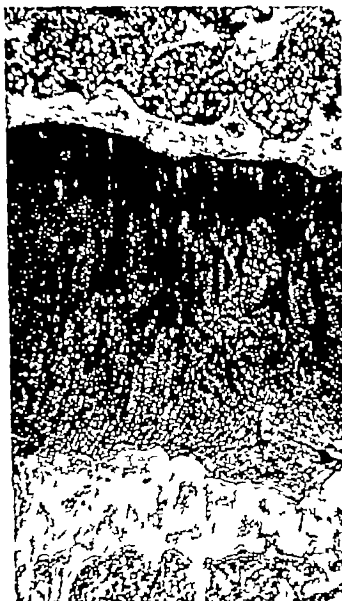
Fig. 174.—Epiphyseal plate of a rachitic animal compared to the normal state. Proximal epiphyseal plate of a rat tibia. (Magnification ×41.)

A. Normal animal.

B Rachitic animal. Note the widening of the epiphyseal plate t almost five times the normal thickness.

tion but with degeneration and necrosis of irregular parts of the overgrown epiphyseal plates. The inadequacy of nutritional supply and the abnormal mechanical stresses in the thickened plates of cartilage may be the causative

factors. The necrotic cartilage is of course replaced by young connective tissue cells of which may form osteoid tissue The same explanation is also valid for observations in human rickets.



B

Fig. 178.—(For complete legend see opposite page.)

The next consequence of the primary changes in cartilage is a retardation, and in some cases a temporary cessation, of growth, which is dependent on endochondral ossification. Because the long bones are greatly affected, the extremities appear short The length of the trunk is not affected quite so much because of the great number of growth centers in the vertebral column. The base of the skull lags in anteroposterior expansion and, in consequence the

forehead seems to bulge. The growth of the mandible is more affected than that of the facial skeleton (Figs. 179 and 180). Rickets seems to be one of the etiologic factors in facial disharmony.

The normal vertical eruption of teeth is dependent on normal growth of the mandibular ramus in height, which provides the necessary space between the upper and the lower jaw. Impairment of cartilaginous growth at the mandibular condyle in rickets will therefore cause retardation of tooth eruption. Since tooth eruption and shedding of the deciduous teeth are also accompanied by resorption of bone and tooth substance, the inhibition of resorption in rickets will constitute a second retarding factor in tooth eruption. Not only

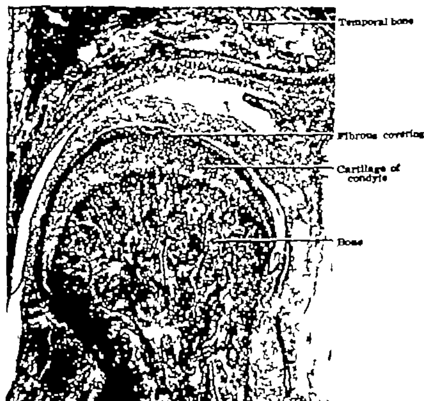


Fig. 179.—Frontal section through the temporomandibular joint of a normal rat. (Original magnification ×44 reduced to ⅔.) (After Weinmann.)

the timing of tooth eruption will be disturbed, but also their positioning since the regular movements of the teeth before and during their appearance in the oral cavity are greatly restricted if bone resorption does not occur at the right time and at the right place. Rickets may therefore cause malposition of the teeth.

Disturbances in calcification of cartilage and of newly formed bone combine to produce other characteristic features of the rachitic skeleton, namely the beading of the epiphyseal regions, most evident at the wrist and ankle, and the rachitic rosary at the costochondral junctions of the ribs. The shaft of most long bones flares at the junction with the epiphyseal cartilage. The addition of new bone at the metaphysis is accompanied by resorption of the

flaring ends of the shaft on the periosteal surface. Only in this way can the central more or less cylindrical portion of the shaft maintain its shape during the period of rapid longitudinal growth In rickets, the addition of new though uncalcified bone at the metaphysis continues, but the modelling resorption ceases because the uncalcified osteoid tissue resists resorption to a high degree. The lack of this modeling resorption results in the clublike thickening of the long bones in the metaphyseal region known as rachitic metaphysis.

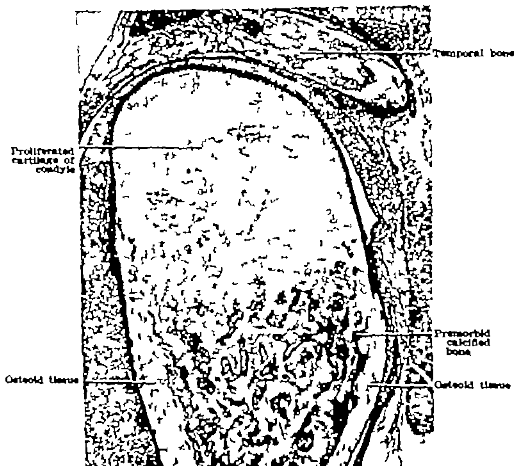


Fig. 180.—Frontal section through the temporomandibular joint of a rachitic rat. Note the thickening of the mandibular neck and the increase in width of the mandibular growth cartilage (Original magnification ×35 reduced to ⅘.) (After Weinmann.)

The deformity is most pronounced in those metaphyseal regions where the shaft normally widens considerably for instance the distal end of the humerus, of the radius, and of the femur and the proximal end of the tibia (Fig 177)

The rachitic rosary results from similar conditions at the costochondral junctions of the ribs. The fact that the beads of the rosary are more prominent on the inner than on the outer surface of the thorax is explained by the important roles which bone resorption on the pleural surface plays in flattening the curve of the growing rib.

Other skeletal changes in rickets are the consequence of reduced me cal efficiency of the rachitic bones. In severe cases, almost the entire shaft bone may consist of osteoid tissue. It is clear that such bones will be break under mechanical stresses, for instance, body weight and muscle Bowleg and knock knee are partly caused by bending of the femur an tibia and fibula and partly by a change in position of the ends of these which are joined to the shafts by overly thick epiphyseal cartilage. So of the ribs leads to characteristic bending at the costochondral junction along the line of origin of the diaphragm, with grave impairment of re tory function. The pelvis, under the weight of the trunk, is compressed n in its anteroposterior diameters. The rachitic deformity of the pelvis is a mon cause of difficulty in childbirth in women who had suffered from vitar deficiency since the rachitic deformities are never entirely repaired in life. Very common also are deformities of the vertebral column, for exa lordosis or kyphosis and scoliosis of varying degree.

Vitamin D deficiency varies with the seasons and the availability of food containing provitamin D In clinical rickets in its most severe many deaths occur and in other cases, the child is dwarfed or crippled fo It is gratifying that large populations once afflicted by this disease are free or almost free from it.

Human rickets is almost always an alternating sequence of episod *severe disease and shorter episodes of partial recovery During the l* periods newly formed metaphyseal bone calcifies, and the bands of calc tion visible as a record of these changes in the roentgenogram are somet referred to as Looser s zones.

Osteomalacia.—The effects of vitamin D deficiency during skeletal gr and after its termination differ After termination of growth, formatic new bone does not contribute significantly to the growth of the skeleton b a factor in the process of replacement of overaged bone by young and bone. To visualize these differences means at the same time to understand two clinical pictures of vitamin D deficiency that is, vitamin D defici in the growing individual or rickets, and vitamin D deficiency in the a or osteomalacia. The causes of vitamin D deficiency in the adult are, of co the same as in the child that is, malnutrition and lack of sunlight. The one additional factor and that is the increase in demands made on the l economy during pregnancy and lactation

The mechanism of osteomalacia is the gradual replacement of well-c fied bone by uncalcified osteoid tissue and thus a *softening of the bo* but not a softening of bone tissue The cause of osteomalacia is, a rickets, primarily a depression of calcium absorption from the *intestinal* tents and secondarily a depletion of phosphorus. The loss of phosphorus is creased by the hyperfunction and hyperplasia of the parathyroids which are leased from the inhibiting influence of vitamin D This leads to a more or severe osteoporosis Unlike rickets, in osteomalacia the osteoclastic resorptio *bone, caused by the secondary hyperparathyroidism,* continues for a long t This difference is explained by the fact that the rapid and more generalized

ition of osteoid tissue in the growing child soon covers the calcified rem ts of bone with a protecting layer Failure of rapid production of new e, on the other hand, *permits* widespread osteoclasis in the adult. In kets, osteoporosis is therefore normally slight, being increased only during iods of temporary recovery when extensive calcification of osteoid tissue l resorption of calcified bone may take place in a relatively short time The nbination of more rapid destruction of well-calcified bone and its slow re-eement by uncalcified osteoid tissue, a characteristic of severe osteomalacia, plains the rapid deterioration of the skeleton.

After a period of vitamin D deficiency parts of bones or entire bones will nsist of osteoid tissue only showing in addition, all the signs of rarefaction. is is the time that those mechanically insufficient elements of the skeleton l be deformed under the influence of pressure and traction. Bowing of ig bones scoliosis of the vertebral column, and deformities of the pelvis are ong the more characteristic symptoms of osteomalacia. In most cases, they accompanied by neuritic pain due to compression of the spinal nerves in intervertebral foramina. Pathologic fractures of the weakened bones are ite frequent.

Hypervitaminosis D

The effects of an overdosage of vitamin D have been described by many thors, but their findings are strikingly contradictory Certain authors de-ribe progressive osteosclerosis combined with metastatic calcification in sev al organs, especially in the kidneys. Others found osteoporotic changes com rable to osteitis fibrosa. Still others believe that osteoporosis is an early age of vitamin D intoxication, whereas later stages are characterized by teosclerosis.

The explanation for these conflicting beliefs is probably the damaging fect of a high dosage of vitamin D on the kidneys. As long as the dosage is ot high enough to inflict severe damage to the kidney the effect of hyper taminosis D is but an exaggeration of the normal effect of vitamin D in estion. The absorption of calcium and phosphorus in the intestinal tract increased and, at the same time the secretion of phosphate by the urine is ecreased by the inhibitory effect of vitamin D ingestion on the parathyroids. n consequence of the rise of the level in calcium and phosphorus in the blood ormation of new bone takes place followed by the deposition of calcium phos-hates in the blood vessels, ligaments, kidneys.

If the tolerance level for vitamin D is passed, the damage to the kidneys will complicate the picture. Phosphates are retained in the body and are now ound in excess of the calcium present. In an attempt to eliminate the relative xcess of phosphorus, the parathyroid glands hypertrophy For a time, the ntagonistic action of the inhibitory factor of vitamin D and the stimulating actor of the hyperphosphatemia will lead to confusing pictures, as observed y some authors. Finally the damage to the kidneys and the resultant hyper arathyroidism will determine the changes in the bones, and it is then that ymptoms of osteitis fibrosa cystica generalisata develop

The extensive damage to the kidney blood vessels, and skeleton which follow vitamin D overdosage are a warning to the physician and the layman *not to use vitamin D promiscuously*

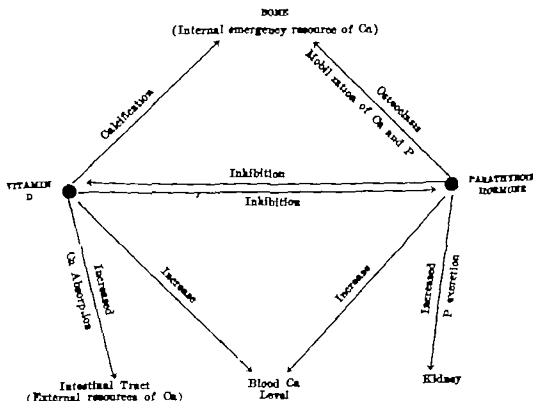
Many authors report also a hypercalcification of bone in hypervitaminosis D This finding needs further confirmation. The greater radiopacity of bones in hypervitaminosis D cannot be accepted as an unequivocal proof of hypercalcification. The calcification of periosteal and endosteal connective tissue, the presence of calcium deposits in the marrow spaces, and the osteosclerosis might be responsible for the greater density of these bones as seen in roentgenograms. The intensive basophilia of the surface layers of bone is not convincing evidence that these layers consist of hypercalcified bone The study of a large material makes it probable that these layers consist of calcified connective tissue The same arguments hold true in evaluating chemical findings.

Parathyroid Hormone and Vitamin D

The parathyroid hormone and vitamin D have a common function to maintain the blood calcium level They achieve this by entirely different mechanisms. In some ways, the parathyroid hormone and vitamin D are antagonistic. The action of vitamin D can be described as increasing the utilization of external, dietary resources of calcium, while the parathyroid hormone mobilizes calcium from internal deposits that is, from bone.

TABLE III

INTERACTION OF VITAMIN D AND PARATHYROID HORMONE



The details of the different action of vitamin D and the parathyroid hormone are summarized in Table III. Vitamin D maintains, or causes a rise of, the blood calcium level by increasing the absorption of calcium from the intestinal tract. It influences by local action the calcification of bone, cartilage dentin, and cementum. Mobilizing external resources, vitamin D restricts the withdrawal from the skeleton of the emergency supplies of calcium by inhibiting the action of the parathyroid glands.

The parathyroid hormone increases or maintains the blood calcium level by withdrawing calcium from the skeleton through the promotion of osteoclastic resorption The excess of phosphorus, necessarily and simultaneously liberated by osteoclasis, is eliminated by the kidney The increase in urinary secretion of phosphorus is brought about by the direct action of the parathyroid hormone on the kidney The parathyroid hormone has, furthermore an inhibiting effect on vitamin D especially on its local, calcifying action.

It is clear that under normal circumstances, the antagonism of vitamin D and parathyroid hormone are resolved into an equilibrium

CHAPTER VII

THE EFFECT OF MINERALS ON BONE AND BONES

CALCIUM
PHOSPHORUS
FLUORINE

CALCIUM

Calcium is indispensable for the development and function of the animal body In man, the daily requirement is about 0.8 grams for an average weight of 70 kilograms During growth and in pregnancy and lactation, greater amounts of calcium are needed. Children up to twelve years of age need about 1 gram per day In the years from twelve to twenty the daily allowance should be 1 4 grams for boys, a little less for girls. The calcium intake during pregnancy should be 1.5 grams and during lactation 2.0 grams. Ninety nine per cent of the calcium found in the body is contained in the skeleton and the teeth and only one per cent in the blood and other tissues. The common foods especially rich in calcium are milk, eggs, cabbage beans, peas, turnips, oat meal, and raisins.

Absorption of calcium from the intestinal tract is regulated by vitamin D Absorption occurs mainly in the upper part of the small intestine. An important role is played by the pH of the contents of the intestinal tract. Most calcium salts are insoluble in alkaline fluids. Acidity of the intestinal contents is, therefore, a prerequisite for normal absorption of calcium. The acidity in the small intestine is raised by the intake of fats. Oxalic acid, contained in spinach, forms insoluble calcium salts and its presence thus prevents calcium absorption Phytic acid, contained in whole wheat, acts similarly Calcium may combine with fatty acids to form soaps if the production of bile or pancreatic juice is disturbed. In such cases, absorption of calcium, fats, and the fat-soluble vitamin D is diminished. The vitamin D deficiency in turn, aggravates the calcium deficiency and a vicious circle is established. The excretion of calcium takes place partly in the large intestine but mainly in the kidney

Calcium is found in the blood in organic compounds as indiffusible calcium and in inorganic salts as diffusible calcium. The former comprises a little less, the latter a little more than one-half the blood calcium The diffusible calcium is almost completely ionized The total amount of calcium in the blood is from 10 to 11 milligrams per 100 cubic centimeters.

Calcium serves a number of functions. As phosphate and carbonate it forms the principal content of bone dentin, cementum, and enamel It is found in all of the other tissues and in all glandular secretions. Two of the

functions of calcium should be stressed. It is necessary for the coagulation (clotting) of blood and it keeps the excitability of nerve endings at a normal level. A calcium deficiency leads to undue excitability, especially of the motor nerve endings, and thus to tetany

The calcium balance is safeguarded mainly by the parathyroid hormone and vitamin D (see page 294)

Since calcium is so readily available, a deficiency should be expected only as a consequence of general malnutrition for example, in famine districts or among the underprivileged. It has been established that about one-half of the American dietaries are below the safety level in calcium intake. In most in stances, the calcium deficiency is caused by a decrease in, or lack of, absorption

The consequences of calcium deficiency in the skeleton are twofold on the one hand the preparatory calcification of the cartilage during the growth period and the calcification of newly formed organic bone matrix are pre vented or greatly disturbed. On the other hand, resorption of bone to mobilize calcium is increased. Either rickets or osteomalacia combined with osteoporosis will result in accordance with the age of the calcium-deficient individuals.

Bone is often described as a storehouse for calcium. This view was justi fied first by the fact that calcium (and phosphorus) may be mobilized by resorption of bone. Moreover the observations on pigeons during the egg laying period were quoted as proof for this contention also the fact that injection of estrogen causes sclerosis of bone in some animals (see page 238) Bone produced during the egg laying period in pigeons or after injection of estrogen is formed in excess of the mechanical needs of the animal, and to inter pret this overproduction of bone as a means of storing calcium salts is entirely justified. This does not mean that the *entire* skeleton can be regarded as a storehouse for calcium salts. It is known that, especially in man, any mobilization of calcium salts from the bone leads to pathologic weakening of the skeleton. There have been, on the other hand, no observations available which would indicate that an overproduction of bone occurs during the first months of human preg nancy to be used as a ready reserve of calcium salts for the needs of the fetus in the last months.

The normal skeleton can, therefore, not be regarded as a storehouse for calcium and phosphorus. It is rather a source of these elements in an emer gency

Because of rapid excretion, overdosage of calcium in normal individuals leads only to a temporary rise in the blood calcium level. A hypercalcemia of long duration is found in primary or secondary hyperparathyroidism, in hyper vitaminosis D and in extensive destruction of bone by tumors. In cases of protracted hypercalcemia deposits of calcium salts, phosphates, and carbon ates, in a ratio of 9 1 can be observed in many organs kidneys, arteries, heart, lungs, mucous membranes. This calcification which is, not quite logically termed metastatic occurs especially in organs and tissues which are rich in phosphates.

Metastatic calcification is not to be confused with dystrophic calcification. The latter a calcification of degenerated or necrotic tissues, has been explained by a local rise in hydrogen ion concentration due to a reduction in carbon dioxide tension. It is, however also possible that in necrotic tissues proteins or mucoproteins experience a depolymerization similar to that postulated in calcification of hard tissues (see page 40) Dystrophic calcification is independent of the local phosphatase concentration.

PHOSPHORUS

Phosphorus, as a constituent of bone and teeth and as an intermediary compound of the carbohydrate metabolism, is, like calcium indispensable for normal function of the animal body The daily requirement of phosphorus in a normal adult is 1.3 grams. Children need slightly less. In pregnancy and lactation the needs are increased. Phosphorus is so abundant in our food that an extrinsic deficiency is improbable

The absorption of phosphorus from the intestinal tract is, in part, dependent on the amount of calcium in the food. If an excess of calcium is present, calcium phosphates which are not readily soluble are formed, and the absorption of phosphorus is retarded to such a degree that most of it is passed in the stool. The presence of fat in the diet, on the other hand can diminish the excess calcium by forming insoluble soaps, and thus it increases, indirectly the absorption of phosphorus.

About two-thirds of the absorbed phosphorus is excreted in the urine. One third contained in the digestive juices, is eliminated in the feces.

Vitamin D since it furthers calcium absorption from the intestinal tract, influences indirectly the absorption of phosphorus. The excretion of phosphorus in the kidney is increased by the action of the parathyroid hormone, which decreases the reabsorption of phosphorus from the glomerular filtrate in the tubules.

The amount of phosphorus in the human blood is between 4 and 5 milligrams per 100 cubic centimeters. Phosphorus is present in the blood in almost equal amounts as inorganic ionized and organic nonionized phosphorus. The organic phosphorus is contained almost entirely in the red blood cells, the inorganic phosphorus in the serum. Eighty five per cent of the total phosphorus content of the body is found in the skeleton and in the teeth.

An extrinsic phosphorus deficiency is possible only in general starvation. An intrinsic phosphorus deficiency is probably always combined with a calcium deficiency An artificial decrease in the phosphorus content of the diet without influencing the calcium intake *leads to significant changes only* if combined with a vitamin D deficiency Experimental rickets in rats is produced by a diet high in calcium but deficient in vitamin D and phosphorus. Why the rat is immune to vitamin D deficiency as such cannot yet be answered.

Intoxication from the presence of elementary or metallic phosphorus has become almost unknown Once it was common, especially in the manufacture

of matches before the inactive red phosphorus was substituted for the toxic yellow phosphorus. The observation of osteosclerosis in patients suffering from phosphorus poisoning led to the use of phosphorus in therapeutic doses in rickets or after fractures in the belief that it would promote bone formation and calcification. Metallic phosphorus in combination with cod liver oil was given as an antirachitic agent. Since the discovery of vitamin D the therapeutic use of phosphorus has ceased.

As an experimental approach to the study of bone physiology and pathology the action of phosphorus has been studied extensively The sclerotic phosphorus bands, which are especially marked after periodic intake of phosphorus, have been, on the other hand, used in determining the rate of apposition of bone in the metaphysis and epiphysis. These bands mark the bone which was formed during the period of phosphorus medication (Figs. 181 and 53)

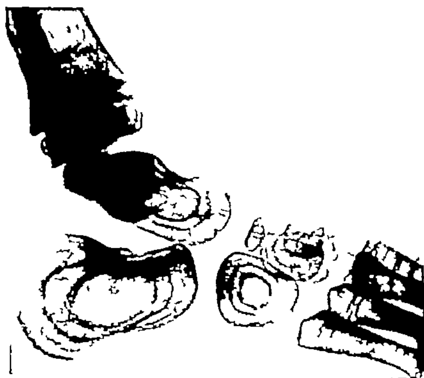


Fig. 181.—Roentgenogram of the foot of a three-year-old boy The child had received phosphorus cod liver oil each winter Three rings of osteosclerotic bone correspond to the periods of medication. (After H. R. Sch rz, W Baensch, and E. Friedl.)

Careful histologic investigations have suggested that osteosclerosis of the growing bone is mainly due to failure of resorption. The disturbance of bone resorption results in the persistence of the primary spongiosa thick trabeculae of bone containing a core of calcified cartilaginous intercellular substance. The metaphyseal trabeculae escape resorption for a long time and thus occupy a greater part of the bony shaft at the expense of the marrow cavity

Observations on adult patients and experimental animals showing a gradual narrowing of the marrow cavity of long bones seem to prove that reduction in, or lack of, resorption alone cannot account for the skeletal changes in phosphorus poisoning. A slowing down of the resorption seems to be accompanied by an increase in bone formation.

Any explanation of the effects of metallic phosphorus ingestion on the bone and cartilage can be only hypothetical. One may assume that phosphorus acts directly or indirectly on the cementing substance of calcified bone. That the altered intercellular substance acts as a foreign body can be deduced from the observations of numerous osteoclasts around bone formed during phosphorus intake. At the same time, the calcified bone is rendered almost unresorbable. The reaction of the surrounding tissue to the "resorption-fast" foreign body" is apposition of bone on its surface in an attempt to encapsulate the damaged tissue. The damage to the matrix and, in turn, the overproduction of bone continue, of course, as long as the phosphorus medication or intoxication lasts.

The necrosis of the jawbones in phosphorus intoxications is, in all probability not primary but caused by the inevitable infections around the teeth or after extractions. The sclerosed and damaged bone tissue then undergoes necrosis and sequestration.

The changes in the bones during clinical or experimental phosphorus intoxication do not seem to be specific. Other metallic poisons, for instance lead and arsenic, cause the development of osteosclerotic bands in the metaphyseal and epiphyseal growth zones which are exactly like the phosphorus bands.

In cases of metallic poisoning the skeleton contains large amounts of phosphorus and lead which in later years are gradually mobilized during the retarded resorption of bone. This fact explains the presence of clinical symptoms of metallic poisoning long after ingestion of the poisonous substance.

FLUORINE

Since the endemic, irregular brown discoloration of the enamel, the mottled teeth, has been recognized as the effect of large quantities (more than 2 parts per million) of sodium fluoride in the drinking water, the influence of this element on the teeth has been the center of attention. The interest in fluorine has been heightened since a relative immunity to caries has been observed in communities where the drinking water contains small amounts of fluorine.

It is interesting to note that the primary change in the enamel is a defect in its calcification, while the brown discoloration of the irregularly distributed areas of hypocalcification is secondary.

The influence of fluorine upon the skeleton has been observed on many occasions. There are, first, the cases of chronic fluorine intoxication in workers in cryolite factories, second, the fluorosis in certain districts of India;

third, a disease of cattle and sheep grazing around factories which use fluorine and, finally a disease of sheep in volcanic areas after the eruption of fluorine containing gases. The changes in the bones in fluorosis have been studie extensively in experiments on rats, dogs, pigs and sheep



A B

Fig. 112.—Osteosclerosis in chronic fluorine poisoning. Roentgenogram of the sternu (After Roholm.)

A, Cryolite worker fifty-one years old.
B Normal individual, fifty years old.

It is interesting that, in communities where drinking water conta fluorides, changes in the skeleton were found only rarely in the United Sta but quite commonly in certain districts in India. The reason for this discr ancy seems to lie in the fact that even the highest observed content of sodi fluoride (8 parts per million) in drinking water though injurious to the enam does not suffice of itself to produce tangible changes in the skeleton. The an

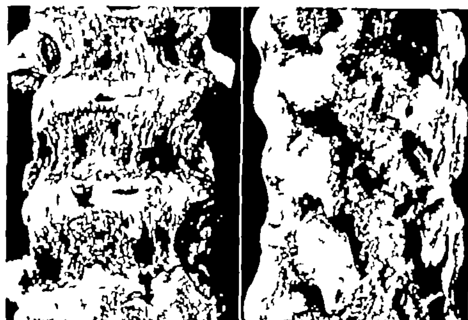


Fig. 183.—Calcification of the periosteum and ligaments in a cryolite worker sixty years old, after twenty four years of work in the factory. (After Roholm.)

A. Lower thoracic and upper lumbar vertebrae.

B. Thoracic vertebrae.

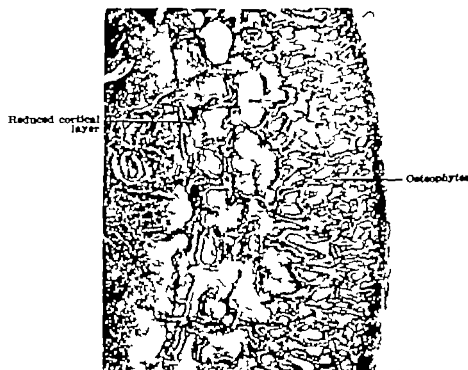


Fig. 184.—Cross section through a long bone of a young dog in experimental fluorosis. Note the reduction of the compact cortical layer and the osteophytic mantel which is actively growing. (After Kellner.)

amount of fluoride, however may cause changes in the skeleton in combination with either dietary deficiencies (vitamin C or vitamin D) or renal damage The people of the fluorotic district in India live, without doubt on an in sufficient diet. In one case of skeletal fluorosis observed in the United States, there was a chronic pyelonephritis.

The findings in spontaneous and in experimental fluorosis are in part contradictory The bones of human patients are diagnosed as sclerotic (Fig 182) Experiments also are said to cause osteosclerosis in some instances. On the other hand, osteoporosis and osteomalacia have been reported in diseased animals and in experiments. These contradictions have been tentatively explained by the differences in dosage and in age. Small doses were said to cause sclerotic changes especially in adults, whereas large doses produce osteomalacia, especially in young animals.

A critical review of the findings casts some doubt on the diagnosis of osteosclerosis if it is made only by roentgen examination and by weighing the involved bones. *Both of these methods may lead to erroneous conclusions*, mainly because of the common occurrence of calcification of the connective tissue adjacent to the bone endosteum, periosteum, blood vessels, and (in man) ligaments (Fig 183) That calcification of periosteal connective tissue is one of the factors leading to diagnosis in 'osteosclerosis is proved by repeated description of the chalky white surface of the bones. It is, of course, impossible to differentiate, by means of roentgenograms, between true osteosclerosis and the increase in calcium content of a bone due to calcification of soft tissues. The same objections are valid for a diagnosis of osteosclerosis based on the weight of a bone A diagnosis of osteomalacia seems also to be doubtful. At most, retarded calcification of rapidly produced osteoid tissue can be observed.

Only the histologic examination can lead to an understanding of the changes in the bone caused by fluorine poisoning The most careful studies were made on dogs which were fed varying doses of sodium fluoride and killed at various times after the experiment was initiated.

These findings can be summarized as follows There is, in all animals, a greatly increased osteoclastic resorption of the premorbid bone In the shaft of long bones, the compact layer has either disappeared or has been broken up into an irregular network of trabeculae (Fig 184) The destruction of the bone proceeds eccentrically toward the periphery At the same time, regenerative and compensatory formation of new bone produces a covering of spongy bone which is immature and coarse fibrillar The formation of these osteophytes which has evidently started on the periosteal surface of the premorbid bone progresses rapidly in young animals. Evidence of this rapid growth are the numerous and continuously arranged large osteoblasts and the rather wide borders of osteoid tissue on the peripheral trabeculae.

Both young and older animals have in common irregularities in calcification of the newly formed bone (Fig 185) and deposits of mineral salts on

the surfaces of the trabeculae The calcification of the osteoid tissue is not homogeneous. Instead, small and large globular areas of calcification are distinctly seen in the intercellular substance

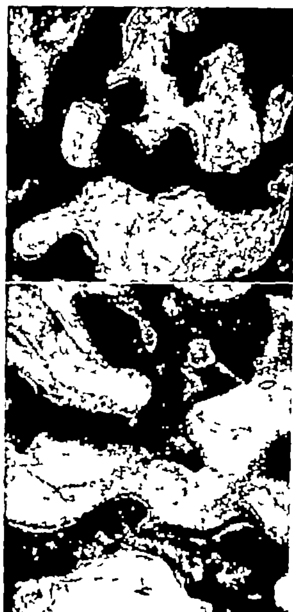


Fig. 126.—Two sections from the skull of a young dog in experimental fluorosis Note the osteoclastic and osteoblastic activity and the irregular calcification. (After Kellner)

The oldest animal of one series showed according to the author not an osteoporosis, but an osteosclerosis of the bones. A critical evaluation of his findings and illustrations reveals that the bones do not present a picture of true osteosclerosis. The bone consisted in this animal, of a rather dense spongiosa with thick trabeculae and narrow marrow spaces, but it was spongy

bone and nowhere could compact bone be found (Figs. 186 and 187) Moreover this rather dense spongy bone had developed from the compensatory osteophytic growth, whereas the old shaft of the bone had been destroyed entirely by osteoclastic resorption, which was still quite active. Many trabeculae in the periphery of this spongy bone were covered by osteoid tissue and osteoblasts, which proves that production of bone was still progressing and that its calcification was possibly retarded.



Fig. 188—Cross section through a long bone of a dog in experimental fluorosis. The animal was older than those shown in Figs. 184 and 185 and received smaller doses of fluorine. The compact cortical layer is not entirely lost and the spongy osteophytes are densely arranged, simulating the picture of osteosclerosis. (After Kellner)

Examination in spontaneous and experimental fluorosis sometimes revealed damage to the kidney if the dosage was high enough to affect the skeleton. The pathologic diagnosis in such cases was interstitial nephritis with loss of active secretory tissue

A survey of the established facts leads to a tentative theory regarding the mechanism of fluorotic changes in the bones. It may be assumed that the presence of fluorides brings about rapid resorption of bone without inhibiting

the formation of new bone. It seems that the presence of fluorides changes the intercellular substance of bone in such a way that formation of osteoclasts results. It is impossible to decide as yet whether this change in the intercellular substance is direct, for example, caused by the presence of fluorapatite instead of apatite or whether the change in the intercellular substance is indirect, that is, caused by a damaging action of fluorides upon the osteocytes.

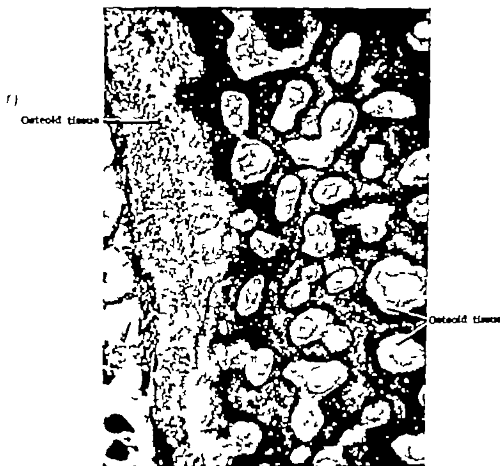


Fig. 187.—Rib of a pig, eight months old, which received 15 mg. of fluorine per kilogram of body weight daily for six months. Note the dense osteophytic proliferation and the wide seams of osteoid tissue. (After Roholm.)

The rapid resorption of bone in fluorine intoxication seems to commence in the marrow cavity of the long bones. This would indicate that in fluorosis the resorption *is an exaggeration of a physiologic activity*. That old bone is resorbed first might suggest that fluorides act primarily on the osteocytes. The rapid and progressive resorption of bone results in the rapid production *of new bone, starting at the periosteal surface of the shaft of the long bones*. The newly formed bone develops in the shape of typical osteophytes, that is, a more or less regular network of trabeculae of immature, coarse, fibrillar bone. This production of osteophytic bone, with its trabeculae radiating from the surface of the old bone and connected by tiers of trabeculae arranged

parallel to the old surface, might be regarded as a compensatory strengthening of the bone. Its particular arrangement and structure are the effect of the speed of the destructive and, therefore, of the reparative process.

The most striking differences between "osteoporotic" bones in young individuals and after high dosage and "sclerotic" bones in older individuals and after low dosage can be explained by the differences in rate of resorption. In young animals and after high dosage, the resorption of bone is very rapid. As a consequence the compact premorbid bone is soon entirely destroyed. The osteophytic "emergency reinforcement" consists of loosely arranged spongy bone which is entirely of the immature type. The numerous osteoblasts and the seams of osteoid tissue along the younger trabeculae testify to the rapidity of osteophytic growth.

After a lower dosage of fluorides and in older persons or animals the destruction of bone is not so rapid, and formation of compensatory osteophytic bone is proportionately slow. In consequence the compact bone is not always entirely destroyed but is partly transformed into spongy bone by widening of Haversian canals; the trabecular network of the compensatory osteophytes is fairly dense and consists not only of immature, but also of mature lamellated bone; the osteoblasts seem to be flatter and the osteoid seams narrower than in young animals. The latter observations, in turn, prove the relatively slow formation of the compensatory bone.

The primary differences between the fluorotic "osteoporosis" and "osteosclerosis" are increased by the different reactions of immature and mature bone during periods of increased resorption. Immature bone is destroyed more rapidly by osteoclastic resorption than is mature bone. The primarily rapid resorption occurring in young animals and after a high dosage of fluoride leads to the formation of immature compensatory bone only. This type of bone is more easily resorbed than mature bone and a vicious circle is established. Just the opposite is true for primarily slow resorption of bone in older animals and after low dosages. The mature bone, which at least in part, constitutes the compensatory reinforcement, is more resistant to resorption than is immature bone, and the already slow process of bone destruction becomes even slower. In adult persons however signs of true, though not severe, osteosclerosis can sometimes be established in microscopic examination, for instance, in the spongy body of vertebrae. It is difficult to reconcile these findings with the experimental evidence. The osteosclerosis might be secondary to the functional changes of the vertebral column after calcification of ligaments and fusion of vertebrae. This question will need further studies.

The chronic destruction of bone tissue is, in all probability responsible for the hypercalcemia and hyperphosphatemia of fluorine intoxication. It seems feasible that this chronic hypercalcemia and hyperphosphatemia are responsible for the "metastatic" calcification of the connective tissue of the bones, arteries, and ligaments.

The disturbance of calcification of the intercellular substance of bone expressed in the precipitation of small and large isolated crystals, may be a consequence of the chemical difference of the mineral salts.

The pathologic picture of fluorosis is further complicated by the frequency of renal damage. In some instances enlarged parathyroid glands have been found. Hypersecretion of the parathyroids, secondary to renal damage, is, in all probability a rather common symptom in fluorosis. In some respects, the presence of fluorine and hyperparathyroidism act similarly upon bone. The final picture is, in many instances, a combination of fluorosis and hyperparathyroidism and the various degrees of parathyroid involvement will cause the great variability in skeletal changes under different and under seemingly similar circumstances.

CHAPTER VIII

HEALING OF BONES

HETEROTOPIC BONE FORMATION

Healing of bones, for instance, after a fracture or after extraction of teeth, occurs by formation of new bone tissue. The biologic details of regeneration of bone have been widely investigated. Clarification of the process of bone regeneration has been aided considerably by the study of spontaneous and experimental heterotopic bone formation. The discussion of extraskeletal osteogenesis will therefore precede the section on healing of fractures. Because of the many similarities in the process of healing the section on fractures will be followed by a discussion of bone grafting

In many animals, bone is formed in organs in which it is not found in man. Bone is found in the sclera in birds, some of which also show extensive ossification of tendons. Many large mammals have a heart bone which develops by ossification of the fibrous septum of the ventricles. Accessory bones are found in the nasal skeleton of mammals having a trunk. Ossification of the cutaneous connective tissue is found not only in reptiles, but also in mammals for example, in the armadillo The tentorium of the dura mater is completely ossified in the carnivores. The corpus fibrosum of the penis, in many mammals, contains a bone, the baculum.

The physiologic development of bone in the tissues of so many organs proves that, phylogenetically at least, the potency of bone formation is universal in the connective tissue of the entire body. The potency of differentiation of connective tissue was not lost during the evolution of the highest mammals, in which, under pathologic conditions or in experimentation, formation of bone occurs in many areas outside the skeleton.

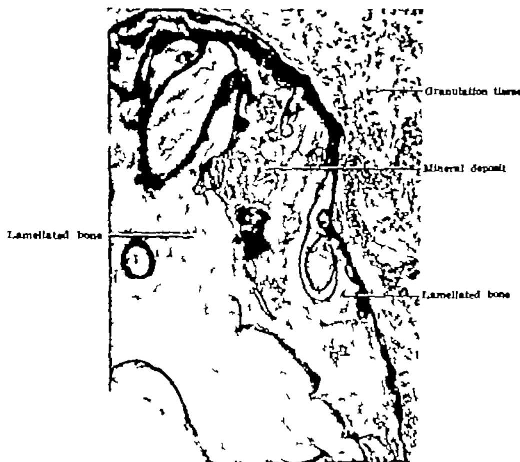
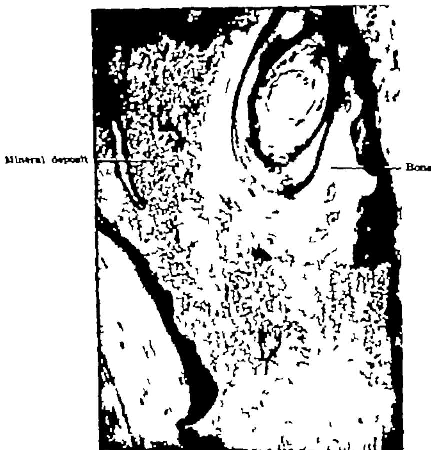


Fig. 13?.—Bone formation in the lung in a case of silicosis. Lamellated bone was deposited upon the remnants of partly resorbed mineralized tissue. Note the granulation tissue surrounding the ectopic bone. (Specimen, courtesy Dr. E. Loeffler.)
A General view. (Original magnification ×125, reduced to ⅗.)
B Detail. (Original magnification ×320, reduced to ⅗.)

Ossification of cartilaginous skeletal parts with age can be termed a normal occurrence. The hyaline cartilage of the laryngeal skeleton can be replaced by bone in its entirety, whereas ossification of the parts consisting of elastic cartilage does not occur. Ossification follows histologically the pattern of endochondral development of bone; that is, the cartilage degenerates, calcifies, is resorbed, and is replaced by bone. It is worth mentioning that ossification of the laryngeal skeleton commences much later in the female than in the male. The cartilaginous parts of the ribs calcify in older persons but are usually not replaced by bone.

True ectopic bone formation has been observed only in tissues which were the site of more or less severe pathologic changes, and all these cases have one common factor namely the reactive proliferation of young connective tissue or granulation tissue. Ectopic bone formation was observed in severely dam aged eyes and in the meninges of the brain, the tonsils, the lungs (Fig 188) the thyroid gland, the ovaries, the uterine tube, the uterus, the penis, the kid neys, the walls of arteries scars of wounds, especially after laparotomy the dental pulp (Fig 189) and, most frequently in the muscles, the fasciae, and the tendons.



B

FIG. 188.—(For complete legend see opposite page.)

Whether we deal with a hematoma, a wound, or a degenerative process of some kind it is important to realize that it is not so much the type of pri mary lesion as the regenerative process common to all, which determines the possibility of ectopic formation of bone.

It seems obvious that formation of bone can occur only if two conditions are fulfilled the presence of cells of low differentiation and therefore of high potentiality and an adequate stimulus to induce these pluripotential cells to differentiate into osteoblasts. Loose connective tissue contains, prob-

ably everywhere reserve cells, the undifferentiated mesenchymal cells of Maximow, whose pluripotentiality is well known. It must be stressed, however that more highly differentiated cells, dedifferentiate before or during cell

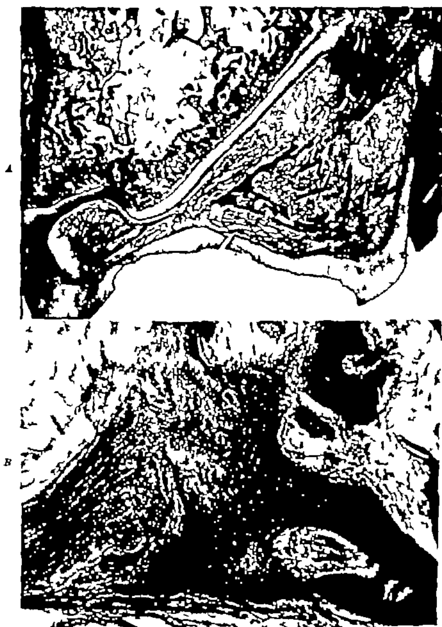


Fig. 189.—Bone formation in the dental pulp. Upper molar of a dog, three months after application of paraformaldehyde (B. Orban.)
A, General view
B Detail in high magnification.

division. Thus dedifferentiation, that is, the loss of differentiation and the release of suppressed potencies can be hypothetically understood as a reorientation, or as the loss, of organoids and the more even distribution of cyto-

plasmic material. These changes are a necessary prerequisite for an equal distribution of cytoplasmic structures to the daughter cells. It can be envisaged that the pluripotentiality of such cells lies in the manifold possibilities of a new arrangement of the components of the cytoplasm.

A visible example of such a dedifferentiation of a highly specialized cell was seen during regeneration of the ciliated epithelium of the frog s pharynx. Not the ciliated cells but the short basal reserve cells divide normally to replace single ciliated cells the excision of a larger part of the epithelium, however increases the rate of cell division and mature cells participate in the process of regeneration. However before a ciliated cell divides cilia and kinetosomes are lost.

In application of these general principles we have to recognize that in proliferating loose connective tissue where reserve cells as well as fibroblasts undergo rapid mitotic division a great number of pluripotential connective tissue cells are present that by the different stimuli can be induced to differentiate into macrophages, or fibroblasts, or chondroblasts, or osteoblasts or remain in their state as reserve cells *

The most common stimulus for the differentiation of osteoblasts seems to be the presence of calcium salts. Bone formation in the lungs, for instance occurs almost without exception around calcified tubercles. Mineral deposits seen in silicosis, may constitute the nucleus of bone formed in the lungs (Fig 188) In many cases the nature of the osteogenic stimulus has not yet been determined for instance in the case of ossification of a hematoma in the stage of organization.

Experimental production of ectopic bone has also shown that differentiation of osteoblasts always occurs in proliferating young connective tissue. This change of character of the connective tissue cells is often called metaplasia, implying a transformation of one tissue into another In reality we deal with the dedifferentiation of cells, and their differentiation in a direction other than their mother cells. It is, however misleading to term a young and less differentiated connective tissue an embryonic tissue or mesenchyme Although the young connective tissue cells have reacquired potentialities which had been partly lost in mature connective tissue it has by no means the great variety of potencies which are characteristic of the true mesenchyme of the embryo The histologic structure of the young connective tissue though simpler than that of mature connective tissue also differs widely from the much more primitive and uniform embryonic mesenchyme.

The stimuli which, in the experiment, induce differentiation of young connective tissue into bone are manifold. Bone may form around implants of bone in connective tissue or around transplanted bone marrow The epithelial cells of the renal pelvis, the ureter and the urinary bladder induce bone formation if grafted into connective tissue muscles, or tendons but not when grafted on liver kidney or spleen. If the proliferation of connective tissue in the bladder

* A discussion of cell dedifferentiation in tumor formation will be found on page 378.

or the kidney is promoted, bone formation may occur in these organs. This can occur in the kidney after ligation of the renal artery and in injury of the bladder during operations. The osteogenic qualities of the transitional epithelium of the urinary organs have been tentatively explained by their high content of phosphatase.

Experiments using transplants into the anterior chamber of the eye of the rat have clarified many points of ectopic bone formation. New bone formation was induced by autogenous transplants of periosteum, bone marrow cancellous bone, cortical bone, fibrocartilaginous callus epiphyseal cartilage, and articular cartilage. Similarly new bone formation followed transplantation of homogenous epiphyseal cartilage to the anterior chamber of the eye.

The formation of bone in these experiments occurred partly from surviving osteogenetic elements of the transplant partly from cells of the host under induction from the transplant. In some instances, irregular masses of bone tissue in other spherical ossicles containing hemopoietic bone marrow were formed.

Bone formation in the dental pulp was seen during the regenerative phase after sterile necrosis of the pulp following application of formaldehyde to the dentin or following the use of diathermy (Fig 189)

FRACTURES

Classification of Fractures

Fractures of bone are caused by trauma of short duration. If the bone is of normal structure, only forces many times greater than physiologic forces or forces which are exerted in an unphysiologic direction can produce a fracture. Such fractures are termed traumatic If the bony structure is changed by disease, such as senile osteoporosis, rickets, osteomalacia, osteomyelitis, hyperparathyroidism and tumors, even physiologic stresses may lead to fracture, which is then termed pathologic fracture (spontaneous fracture)

A fracture is termed incomplete or complete according to whether it leads to partial or to complete discontinuity of the bone. In the latter case, the fragments can be approximated or displaced. The most severe injury to a bone leads to a comminuted fracture. Here, the bone is splintered at the site of impact, and smaller or larger fragments of bone are found between the two main fragments. If the site of fracture communicates with the outside through a wound of the overlying parts, the fracture is termed *compound* or *open*. When the fracture is protected by the skin, it is termed simple or closed.

The sequence of the stages in the healing of fractures will be discussed first in cases of simple traumatic fracture, on which a wealth of detailed knowledge has been accumulated in the last century Subsequently complications and disturbances of the typical pattern of bone healing will be considered.

Healing of Simple Traumatic Fractures

Gross Anatomic Findings.—The rupture of blood vessels in the bone marrow and in the periosteum, and sometimes in the adjacent muscles, causes the

development of a large hematoma around a fracture, the bleeding extending into the bone marrow and into the surrounding soft tissues. The blood of the hematoma coagulates from six to eight hours after the accident. Later the adjacent tissues show an active hyperemia and edema. The hyperemia may last for several weeks. The blood clot is soon organized and gradually transformed into a callus. The callus increases in size from four to six weeks after the injury and then diminishes gradually. In favorable cases, the site of the fracture is not recognizable after a period of three to four months. The mobility of the fragments, which is characteristic for most fractures diminishes when callus formation is well under way.

Histologic Findings.—The knowledge of histologic changes occurring during healing of fractures was derived primarily from experiments on animals. Many observers doubted whether these findings could be applied to man. In recent years, extensive studies carried out on human subjects have shown that the general pattern of bone repair in man is the same as that in experimental animals. Generally healing of a fracture involves formation of cartilaginous callus. The lack of cartilage during bone healing was ascribed by some observers to differences in the development of various bones. Membrane bones are said to heal without cartilage formation.

Other investigators asserted that a cartilaginous callus is formed only if the fragments are subjected to pressure, whereas, under tension, only membrane bone formation takes place. All these theories have not as yet been substantiated. The failure of cartilage formation during bone healing can therefore be described as a deviation from the normal pattern.

During the healing of fracture, six stages can be observed

1. Clotting of blood of the hematoma.
2. Organization of the blood clot.
3. Formation of fibrous callus.
4. Formation of primary bony callus.
5. Formation of secondary bony callus.
6. Functional reconstruction of the fractured bone

These phases will be described exactly as if one followed another in orderly sequence. It has to be emphasized that the different stages overlap considerably for example, the formation of a bony callus may be proceeding in the periphery whereas, in the center organization of the clot is still under way.

Fibrous or Temporary Callus.—A fracture is surrounded by a hematoma in which fragments of periosteum muscle fascia, bone, and bone marrow may be found. During coagulation of the blood in the hematoma, a meshwork of fibrin is formed. The fragments of tissue enclosed in the blood clot for the most part degenerate or disintegrate. Some may survive and play a role in the reparative process. Muscle fragments show fibrous degeneration, necrosis, and autolysis. Bone marrow undergoes fatty degeneration. Small isolated bone fragments necrotize. Necrosis of bone is not restricted to these fragments but is always found at the fracture line (Fig 190) extending from there along the endosteal and periosteal surfaces for a variable distance.

Replacement of the blood clot by young connective tissue (granulation tissue) results in the organization of the blood clot. It is initiated by chemical stimuli arising from the breakdown of proteins. It can be shown that an aseptic wound will not heal if the blood clot and debris are entirely removed and the wound is completely protected from irritation



Fig. 164.—From an experimental fracture of a tibia of a cat. Necrosis of bone at the fracture line and consecutive resorption. (Original magnification ×160 reduced to ⅝.)

The reparative changes begin with a reaction of the blood vessels and the surrounding connective tissue. The blood vessels, arteries, veins, and, finally the capillaries, dilate and the blood stream is slowed, a marked hyperemia resulting Blood plasma exudes from the capillaries. The white blood cells accumulate at the walls of the capillaries and remain in contact with the swollen endothelial cells. Later leucocytes and lymphocytes pass through the capillary walls into the surrounding tissue and from here enter the blood clot. The next step in the reaction of the vascular system is the proliferation of the capillaries which invade the blood clot. Lymph capillaries are assumed to grow into the blood clot alongside the blood capillaries.

The connective tissue surrounding the hematoma reacts first by a differentiation of phagocytic macrophages or polyblasts. These cells derive from resting wandering cells, histiocytes, or adventitial cells and from the undifferentiated, pluripotential cells of the connective tissue which normally are found close to small blood vessels and capillaries. Together with the macrophages, proliferating fibroblasts invade the blood clot where they produce a network of reticular argyrophil fibers.

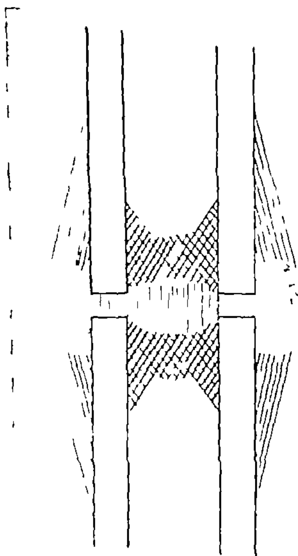


Fig. 191.—Diagram of the callus in a simple fracture of a long bone. Obliquely hatched, anchoring callus; stippled, bridging callus; cross hatched, sealing callus; vertically hatched, uniting callus.

The time needed for organization of the hematoma and its replacement by granulation tissue is variable, depending largely on its size. Organization may be complete as early as the end of the first week but may require from thirty to sixty days.

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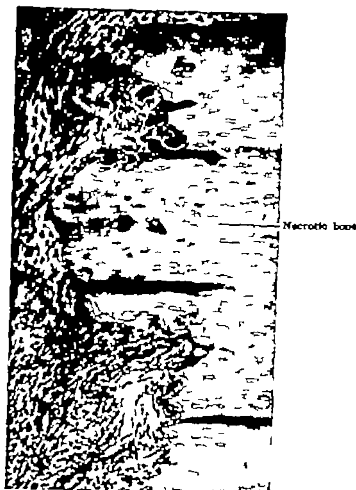


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The connective tissue surrounding the hematoma reacts first by a differentiation of phagocytic macrophages or polyblasts. These cells derive from resting wandering cells, histiocytes, or adventitial cells and from the undifferentiated pluripotential cells of the connective tissue which normally are found close to small blood vessels and capillaries. Together with the macrophages, proliferating fibroblasts invade the blood clot where they produce a network of reticular argyrophil fibers.

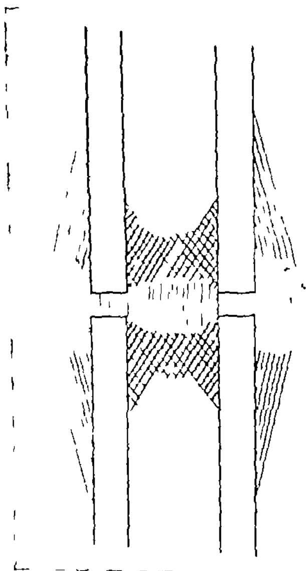


Fig. 191.—Diagram of the callus in a simple fracture of a long bone. Obliquely hatched, anchoring callus; stippled, bridging callus; cross hatched, sealing callus; vertically hatched, uniting callus.

The time needed for organization of the hematoma and its replacement by granulation tissue is variable, depending largely on its size. Organization may be complete as early as the end of the first week but may require from thirty to sixty days.

A.

B.

Fig. 192.—Beginning formation of the anchoring callus two weeks after experiment fracture of the tibia of a cat. After initial resorption, *A* bone formation sets in under pr liferation of young connecti e tissue, *B* (Magnification ×170)



Fig. 193.—Advanced stage in formation of anchoring callus three weeks after experi mental fracture. Note the trabecular arrangement of the primitive bone. The trabecula are lined with active osteoblasts the marrow spaces filled with young cellular connective tissue. (Original magnification ×170 reduced to ½.)

The primary function of granulation tissue is removal and replacement of necrotic tissues. Macrophages and polymorphonuclear leucocytes perform this function by their phagocytic activity and remove the engulfed particles by way of the lymphatics. Bone fragments are removed by osteoclasts which differentiate from invading cells of the connective tissue.

The granulation tissue develops into loose connective tissue as soon as its primary function has ended The macrophages and polymorphonuclear leucocytes gradually decrease in number The capillaries are partly obliterated after the hyperemia has receded The fibroblasts now play the most important role, producing numerous collagenous fibers, most of which are parallel to the long axis of the bone The tissue which is now formed is termed fibrous or temporary callus, or procallus.

PRIMARY BONY CALLUS.—The fibrous callus forms a spindle shaped cuff around the fracture area extending to a considerable distance along the two fragments filling the cleft between the fragments and sealing the marrow cavity of each fragment more or less completely For the purpose of description it seems convenient to divide this callus into different areas The callus surrounding the fragments themselves has been termed periosteal callus. The term *anchoring callus* seems to be more appropriate, since the callus is not formed by the periosteum alone It secures the connection of the callus to the fragments. The callus replacing part of the bone marrow has been termed endosteal callus. This callus closes the opened marrow spaces toward the fracture line and should be termed *sealing callus* The tissue between the fragments has been called intermediate callus. A more descriptive term, *uniting callus* is suggested for this part of the callus. Finally the most voluminous part of the callus circling the fracture area itself, frequently referred to as ensheathing or parosteal callus, will be termed *bridging callus* (Fig 191)

The replacement of the fibrous callus by bone occurs in typical fractures of tubular bones partly by direct bone formation. This type of ossification is seen in the anchoring, sealing and uniting callus, which are not directly subjected to stress especially shearing forces. The bridging callus develops in an area which is always under mechanical stress. Here, the formation of bone is preceded by the formation of cartilaginous tissue, which is replaced by bone The formation of the bony callus normally follows a *typical pattern as to time* The anchoring callus is the first to form. Then follows the sealing callus, later the bridging callus, and last the uniting callus.

Anchoring Callus—The anchoring bony callus develops at the point farthest from the line of fracture, proceeding toward the region of the bridging callus (Fig 192) Young and therefore, pluripotential connective tissue cells of the fibrous callus differentiate into osteoblasts and produce spongy bone which is in direct connection with the surface of the bone fragments. The trabeculae of the spongy bone are more or less parallel to one another and at acute angles to the long axis of the fractured bone they are connected by short crossbars (Fig 193) The tissue in the spaces between the trabeculae does not change its character remaining as fibrous marrow

Sealing Callus—The bony callus inside the compact cortical layer of a long bone develops at some distance from the plane of fracture (*Fig. 194A*). It is rarely as far away from the fracture line as is the anchoring callus. Toward the fracture line it increases in volume, protruding more and more into the marrow space. Finally a more or less complete bony plate is formed,

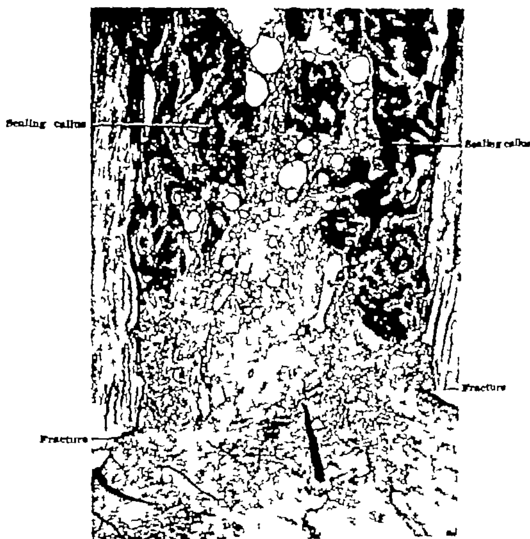


Fig. 194A.—Sealing callus, three weeks after experimental fracture. Primitive bone in trabecular arrangement, growing out from the inner surface of the compact cortical bone. Part of the marrow space filled with loose connective tissue. (Original magnification ×18; reduced to ⅝.)

sealing the marrow space toward the tissue between the bone fragments (Fig 194B). The osteoblasts producing the sealing callus are also differentiated from cell elements of the young connective tissue. The sealing callus consists mostly of irregularly arranged trabeculae of bone.

Bridging Callus—During the time of formation of the anchoring and sealing bony callus the connective tissue of the bridging callus differentiates into fibrocartilage and, later hyaline cartilage (Fig 195). The ossifi

cation in this area does not begin until the spongy bone of the anchoring callus has reached the cartilage From then on the cartilage is gradually replaced by bone (Fig 19C) The cells of the cartilage enlarge and the intercellular substance calcifies and is resorbed by the cells of the proliferating connective tissue Many trabeculae of calcified hyaline substance persist for a time and protrude into the growing connective tissue Osteoblasts differentiating from the cells of this tissue form layers of bone surrounding the spicules of calcified cartilage and in this way build spongy bone. This process

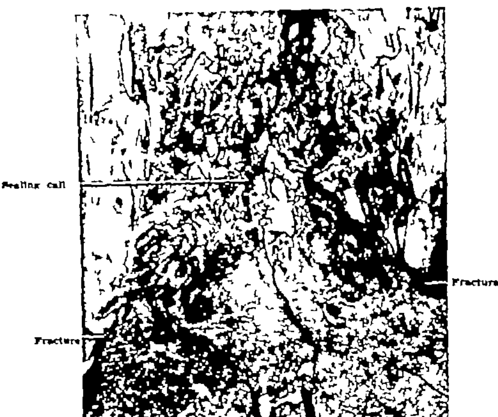


Fig 194B —Sealing callus three weeks after experimental fracture Marrow cavity filled with spongy bone to the plane of fracture (Original magnification ×30 reduced ⅓)

of endochondral bone formation proceeds from both ends of the bridging cartilage until the bony bridge is complete and anchored to the bone fragments by the callus.

Uniting Callus—The fibrous tissue between the two fragments remains unchanged for a long time Its ossification begins only when the other parts of the bony callus are already far advanced toward consolidation Bone formation in the uniting callus occurs by direct ossification In rare instances, islands of cartilage have been observed in this region. The formation of the uniting bony callus is never just an ossification of the connective tissue interposed between the fragments. More or less extensive resorption of the oppo-

site ends of the fragments takes place concomitantly with the formation of the fibrous callus itself. The uniting callus then fills the developing irregular spaces and thus is firmly anchored to the main fragments of the bone

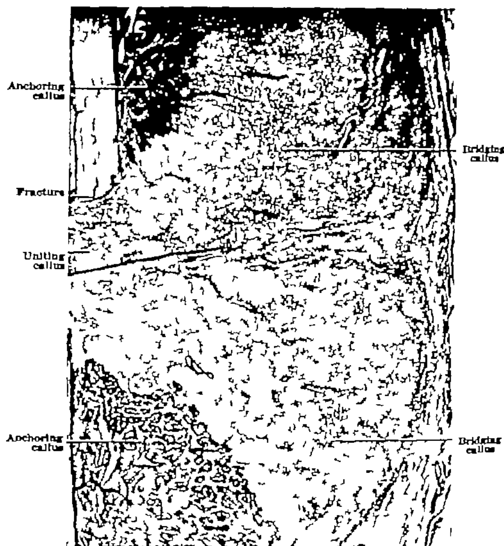


Fig. 195.—Bridging callus two weeks after experimental fracture of the tibia of a cat. The bridging callus consists of cartilage and some connective tissue. It is being replaced by primitive bone from the anchoring callus. (Original magnification X30 reduced to ⅘.)

Structure of Primary Bony Callus and the Roentgenogram.—There is a marked discrepancy between the histologic and the roentgenographic appearance of callus. Even at a time when histologic examination reveals advanced bone formation, the callus is not yet visible in the roentgenogram. The primary bony callus, because of the immaturity of the bone at this time, is so radiolucent that it cannot be distinguished from the surrounding soft tissues. The primary bony callus consists of coarse fibrillar bone (Fig 197) the osteocytes of which are numerous, large and irregularly distributed in the

matrix The intercellular substance itself contains bundles of thick fibers which form an irregular network That the mineral content of coarse fibrillar bone is appreciably lower than in lamellated bone can be proved easily by the fact that this bone can be cut with a knife without previous decalcification The trabeculae of the primary callus, whether they develop directly or replace cartilage are surrounded by a layer of osteoid tissue In fast growing bone calcification lags behind formation of the matrix even under normal metabolic conditions

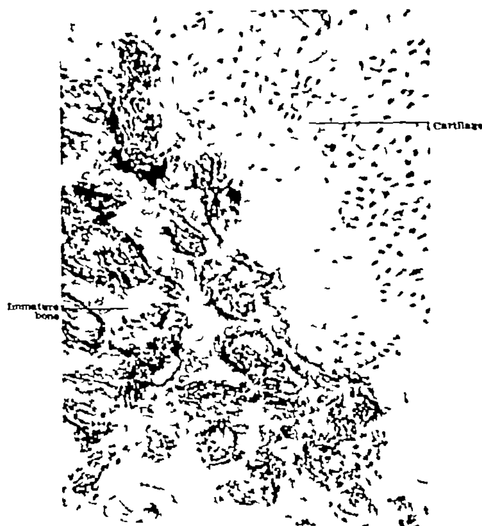


Fig 196.—Detail of section shown in Fig. 195. Border between cartilaginous and bony callus. (Original magnification X170) reduced t ¼.)

SECONDARY BONY CALLUS.—The next stage in the healing of a fracture is the replacement of primary by secondary bony callus (Fig 198) Two processes occur simultaneously in this phase (1) the resorption of immature, coarse-fibrillar bone and its replacement by mature lamellated bone and (2) the functional reconstruction of the loose spongy bone of the primary callus into the much denser secondary callus by the formation of compact bone

in certain areas. This process begins at a time when at least the larger part of the cartilaginous bridging callus is replaced by immature bone, and thus a temporary bony union of the larger fragments is established. During the replacement of immature by mature bone, parts of the coarse fibrillar bone may at first escape resorption, and they are then found embedded in the lamellated bone. The progressive reconstruction of the secondary bony callus by resorption and apposition will eventually lead to the disappearance of all remnants of immature bone



Fig 197—Osteoclastic resorption of primitive bone in the callus two weeks after experimental fracture of the tibia of a cat. (Original magnification ×170; reduced to ⅘.)

When formation of the secondary callus begins, the callus becomes visible in roentgenograms and the progress of its formation can be followed by roentgenographic examination This is possible because of the greater mineral content of the mature bone as compared with the immature bone and the formation of areas of compact bone, replacing the spongy bone of the primary callus.

Functional Reconstruction of the Healing Bone.—During callus formation, bone is produced in excess as a protective measure. It is interesting that, as a rule the volume of the callus is greatest at the concavity if the bone fragments are not perfectly aligned. This affords protection against further angulation of the fragments and perhaps results from bending forces acting upon the forming callus. After solid reunion of ideally adapted fragments, the surplus bone, surrounding the site of the fracture as a thick spindle loses

its functional importance. It is then gradually reduced and finally removed by resorption until the original shape and outline of the fractured bone has been re-established. This process of resorption of bone which is not under mechanical stress is in agreement with the knowledge of development of the normal skeleton.

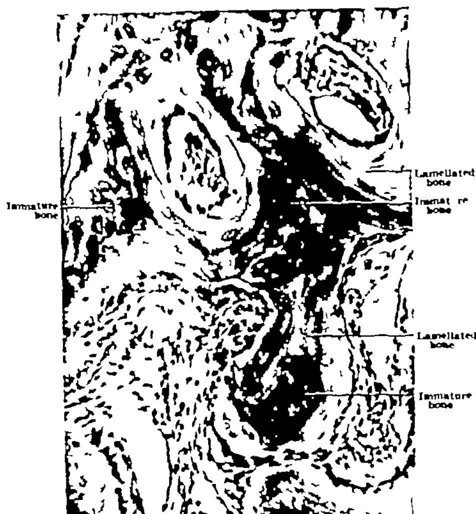


Fig. 1[illegible].—Formation of lamellated bone around remnants of primitive bone in the callus 6 weeks after experimental fracture of the tibia of a cat. (Original magnification ×290 reduced to ¾.)

In a case of ideal adaptation of the fragments of a fractured bone the site of a previous fracture cannot be detected by gross anatomic or roentgenographic examination. In the majority of the cases the alignment of the fragment is, though clinically and functionally satisfactory, not ideal. In these cases, the bone, including the callus, is remodeled according to functional stresses. Parts of the callus are removed, parts of it are involved in the process of internal reconstruction and incorporated into the reshaped bone and the original fragments themselves are molded by resorption and apposition which may extend

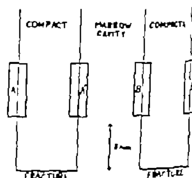


Fig. 109.—Beginning adaptational reconstruction two weeks after experimental fracture of the tibia of a cat (Magnification X110.) Longitudinal sections of the shaft of the tibia at the nearest point 13 millimeters from the fracture line (see diagram)

A Periosteal surface with osteophytic appos tion of bone.

A' Marrow surface with osteoclastic resorption.

B Opposite surface of the marrow ca ity with osteophytic apposition of bone

B' Periosteal surface with osteoclastic resorption.

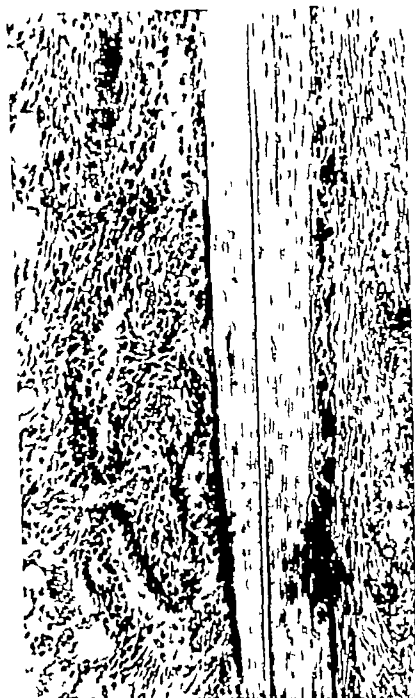


Fig. 109.—(For complete legend see opposite page.)

into areas far from the site of the fracture and far beyond the enveloping callus (Fig 199) The functional reconstruction of the callus is a slow process, even under favorable conditions, continuing through many months and even years.

Healing of Pathologic Fractures

Pathologic fractures may be defined as fractures of a diseased bone. The ultimate fate of such a fracture will depend on the underlying pathologic process Pathologic changes may be of local origin and therefore be restricted to one bone, or they may be of systemic origin and will then involve several bones or the entire skeleton Reports on the healing of pathologic fractures are, in many cases incomplete or controversial The discussion here will be confined to those diseases of bones which have been studied extensively

Osteoporosis may be generalized, as in old age, or it may be caused by disuse, for example immobilization, and it is then confined to single bones. Senile osteoporosis is caused by a decline in bone formation as part of the decrease in cellular activity of old age. Spontaneous fracture of the bone the structure of which had been weakened by disuse, occurs when the skeletal part, so changed, is again subjected to function. Under the influence of renewed function, fairly normal callus formation can be expected.

A callus forming after fracture of a bone rarefied by hyperparathyroidism is subjected to the same pathologic influences as the entire skeleton. The callus will, therefore, form in fairly normal amount and at fairly normal speed, but the bone thus formed will soon fall prey to resorption.

The presence of primary or metastatic tumors may weaken a bone to such an extent that it fractures under physiologic stress. In such cases, callus formation will be dependent on the balance between the growth and the development of the callus and the growth of the tumor If the tumor expands slowly satisfactory consolidation can be expected for a time. With a rapidly growing tumor callus formation may be prevented altogether

Rickets is characterized by a lack of calcification of cartilage and of newly formed bone although bone formation per se is unimpaired. The changes in a callus after fracture of a rachitic bone are identical to those seen in the entire skeleton. Fibrous and cartilaginous callus will develop as in normal cases. Formation of osteoid tissue in the fibrous callus will proceed at a normal rate but the osteoid tissue will not calcify Formation of endochondral bone which should replace the cartilaginous callus will not occur because the hyaline cartilage does not calcify and therefore is not removed by the cells of the proliferating osteogenic tissue In experiments, spontaneous calcification of the cartilage and of newly formed osteoid tissue has been observed in rachitic animals, but it is always abortive It has been maintained that the calcium salts are liberated from the bone resorbed during internal reconstruction after the fracture and that the mineral salts are transported to the tissue of the callus.

The success of treatment of a pathologic fracture will depend entirely on one's ability to influence or overcome the etiologic factors. One cannot

expect to influence senile osteoporosis. Osteoporosis caused by disuse may be influenced by physiotherapy. Extirpation of the parathyroid tumor which has caused Recklinghausen's disease will lead to consolidation of any fracture incurred during the time of active pathologic change (Fig. 150). Antirachitic therapy with vitamin D will lead not only to healing of rickets but also to the ossification and calcification of a previously soft and deficient callus.

Attempts to speed bone healing in normal healthy individuals by medication have failed. Neither calcium phosphorus nor vitamin D therapy has any effect on callus formation in persons with a balanced mineral metabolism. In such cases, the processes of bone formation and calcification are optimal and cannot be hastened by the addition of any element in excess. Overdosage with vitamin D not only is ineffective but also may be outright injurious. Massive doses of vitamin D may cause renal damage and generalized osteoporosis, which involves the forming or already formed callus to the same degree as any other part of the skeleton.

In cases of retarded calcification of the callus, the cause may be sought in a relative vitamin D, calcium or phosphorus deficiency since such cases respond very readily to appropriate therapy.

Variations in the Healing of Fractures

The preceding description of the healing of fractures is based on the wealth of material, clinical and experimental, on fractures of the shaft of the long bones. Histologic observations on the healing of fractures of other bones are few but the information at hand justifies the following brief statements.

The development of sealing callus is dependent on the presence of a wide marrow space. Where this is lacking, as in flat bones, without a greater amount of spongy bone sealing callus *does not form.*

Fractures of the bones of the skull, especially of the vault, *show retarded* and reduced callus formation. Very often the fragments do not undergo bony union but remain united by dense connective tissue which connects the external periosteum with the dura mater. This persistence of fibrous uniting callus cannot be regarded as evidence of failure of functional healing since these bony fragments are often immovably fixed by their connection with the neighboring bones.

The absence of a cartilaginous phase during callus formation in the skull which has been observed frequently, has been explained by some authors on the basis of differences in the ontogenesis of bones. Cartilaginous callus was thought to be absent in bones which develop by membranous ossification. This is *not correct.* Cartilaginous callus is absent in the healing of fractures of the body of the scapula, an endochondral bone. On the other hand, cartilaginous callus has been known to develop in the healing of experimental fracture of the mandible, a membrane bone. It seems more logical to assume that the mobility of the fragments and the presence of shearing forces at the site of the fracture are responsible for the formation of cartilage and that cartilage does not form where these mechanical stimuli are absent.

Healing of Compound Fractures

If a compound fracture area is not infected, the healing of the fracture itself will start simultaneously with healing of the superficial wound and will proceed in the same way as in a simple fracture.

All infected compound fractures will show considerable disturbance in the process of healing mainly because of damage to the tissues at the site of fracture, manifested by the development of a purulent periostitis and osteomyelitis (Figs. 211 and 212) In such cases, resorption of necrotic bone areas and apposition of new bone are retarded or even become impossible. The formation of new bone can take place only at the periphery of the infected area and may even be excessive, leading as in the case of osteomyelitis, to the formation of an involucrum. Resorption of bone starts at the boundary between necrotic and undamaged bone, thus leading to formation of a sequestrum. Smaller isolated fragments of bone in an infected compound fracture invariably become necrotic and are exfoliated or have to be removed

The outcome in a compound fracture will depend on the duration of the infection and on the amount of bone lost at the site of fracture. Formation of callus may start when the acute infection subsides and becomes chronic. In cases of prolonged infection or cases of too great loss of bone a bony union will not be achieved and pseudarthrosis will develop

Pseudarthrosis

A nonunion of movable bone fragments is called pseudarthrosis. The reasons for the failure of bony union are manifold infection of a compound fracture excessive mobility of the fragments, interposing of soft tissues between the fragments and, finally a decrease in regenerative capacity of the patient for instance, in old age or an excessive width of the gap between the fragments.

The simple type of pseudarthrosis is characterized by a fibrous union of the fragments. Sealing callus develops in most of these cases even to a greater extent than in normal healing of fracture In cases of longer duration the surfaces of the fragments are smooth plates of compact bone originating from the spongy sealing callus Under the influence of the shearing forces, at the site of the fracture the fragments of the bone can be covered by a layer of fibrocartilage or even hyaline cartilage which has differentiated from the connective tissue between the fragments. The presence of cartilage in a pseudarthrosis can be regarded as a step in functional adaptation to a new pathologic joint.

Functional adaptation can proceed even farther with the appearance of irregular cavities in the connective tissue between the fragments. These areas may finally extend through the entire width of the fractured bone The cavity thus formed is bounded by the cartilaginous covering of the fragments and by a sleevelike ligament connecting the fragments at their periphery In such cases, the inner layers of this ligament show a structure which is, in many details, that of the synovial capsule of a true joint. This type of pseudarthrosis has been termed nearthrosis (Fig 200)

Cartilage

Capsule

Nearthrotic cavity

A



B

Fig. 209.—Nearthrosis in a fractured rib. Note the formation of cartilage synovial capsule, and a true articular space.

A. General view

B. Detail under high magnification.

Sudeck's Atrophy of Bone

After fracture of a bone a peculiar rapid loss of bone tissue in the immediate neighborhood of the fracture, but also in the bone and bones distal to the fracture line, has been observed and is known as posttraumatic or Sudeck's atrophy However the same changes may be observed in diseases of joints and of soft tissues, as for instance osteomyelitis, arthritis, cellulitis, and also in paralysis and painful nerve lesions, for example causalgias.

The pathogenesis of Sudeck's atrophy is not fully understood. The commonly accepted but hypothetical explanation rests upon the analysis of the common denominator in all the injuries and diseases in which Sudeck's atrophy may develop namely the spontaneous or therapeutic immobilization of an extremity It is assumed that the loss or restriction of function leads to the loss of muscle contraction as an auxiliary force for venous and lymphatic circulation and thus to a passive hyperemia in the immobilized area.

The hyperemia of marrow spaces leads to pressure atrophy of the spongiosa and sometimes even of the corticalis of the involved bones.

HEALING OF WOUNDS AFTER TOOTH EXTRACTION

In many respects, the healing of an extraction wound resembles that of a fracture It therefore seems logical to discuss this phenomenon in connection with the reparative processes following the fracture of a bone.

It is clear that all extraction wounds communicate with the oral cavity The danger of infection seems great and the rarity of such an infection can be explained by the antibacterial and cleansing action of the saliva.

The steps in the healing of an empty socket are, in principle, the same as in the healing of a fracture

1. Formation of a blood clot filling the socket.

2. Organization of the blood clot by proliferating young connective tissue.

3 Gradual replacement of the young connective tissue by coarse fibrillar bone.

4. Reconstruction of this region of the alveolar process by resorptive activity on the one side and replacement of the immature bone by mature bone on the other

5 As in a clean compound fracture epithelization and healing of the surface wound occurs simultaneously with the other reparative processes.

The formation and undisturbed organi... a blood clot are of prime importance. The blood ... can be regarde... fect culture medium for the proliferating cel... young connec... which invade it in the very first days after t... on (Fig. 201) ... me time, th... lot serves to protect the more o... d surface o... ocket F... of for mation or early remo... od clot lea... cations l... ling of the socket. In such ... which is k... socket ... the d... alveolar bo... are slo... hy... ing

resorption. During this time the condition of the alveolar bone suggests localized inflammation. The filling of the socket takes a long time because the proliferating granulation tissue is exposed to insults of chemical, mechanical, and bacterial nature. The dry socket is always characterized by excessive pain of long duration.

In the roentgenogram the socket remains visible as a "defect" in the bone for many months although histologic investigations have proved that it is filled by bone in the second month. This discrepancy is the result of radiolucency of the immature coarse fibrillar bone filling the socket (Figs. 202 and 203). As was mentioned, replacement of immature by lamellated bone is tardy.

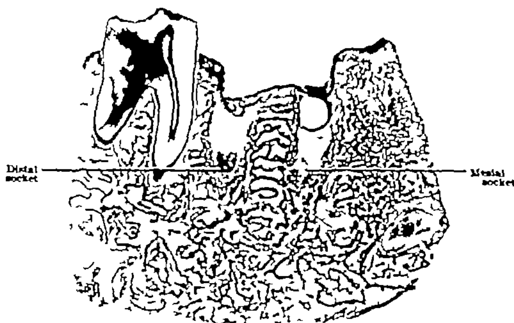


Fig. 201.—Sockets of a lower second molar about six weeks after extraction. Male sixty-seven years old. Fairly advanced healing. Blood clot organized with exception of a small area in the distal socket. Formation of immature spongy bone in the apical half of the sockets. The empty subepithelial spaces are small abscess cavities. (Magnification X2.) (After Claflin.)

The reconstructive process (Fig. 204) which starts soon after the first three phases of healing are completed is governed by the *change in functional stress* in the alveolar bone and leads generally to loss of bone in the area and to the formation of a compact lamella at the surface of the bony scar (see page 198). If one tooth is extracted while its neighbors continue to function, the loss of bone substance is not extensive. Only if a *group of teeth* are lost an almost total disappearance of the alveolar process can be observed. The reconstruction is often complicated by the movement of adjacent teeth into the empty space. In such cases, part of the scar is again rebuilt to form the sockets of the drifting teeth.

In the premolar and especially the molar region of the upper jaw reconstruction of the scar in the alveolar process is often accompanied by changes in the maxillary sinus. The replacement of mechanically superfluous bone tissue may occur here to some part by extension of a recess of the maxillary sinus into the scar. In such cases, the alveolar bone at the site of extraction may finally be reduced to a rather thin plate of compact bone (Fig. 78).

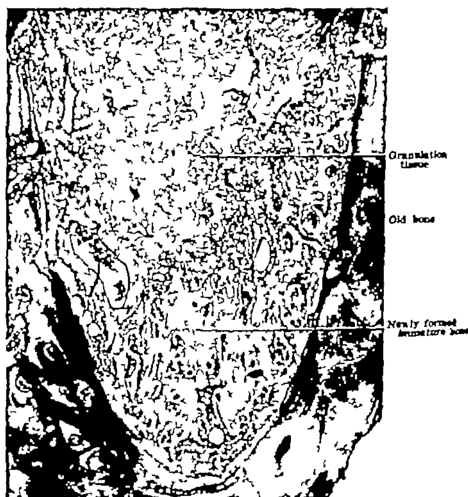


Fig. 201.—Socket of a lower second premolar three and one-half weeks after extraction. Blood clot organized. Formation of spongy immature bone actively progressing. Note the difference between lamellated alveolar bone and the fast-growing immature bone inside the socket. (Original magnification ×80, reduced to ⅔.) (Courtesy Dr. H. Pendleton.)

Bone Grafts

The replacement of lost parts of a bone by implantation of bone or a substitute for bone has been studied extensively. The results of these studies are in accord with our knowledge of bone repair and of functional adaptation and reconstruction of bone. There are four methods of repair of defects of bone. The method is called autoplastic if bone of the patient or the experimental animal is transplanted into the defect. If bone of the same species is grafted from one individual to another the grafting is called homoplastic. The graft

is called heteroplastic if bone of a different species is used and alloplastic if instead of bone a substitute is employed for instance ivory or a mixture of calcium salts.

The most favorable results can be expected in an autoplastic operation especially if the surgeon succeeds in keeping a part of the transplant alive The vitality of transplanted bone depends on the surface area of the trans

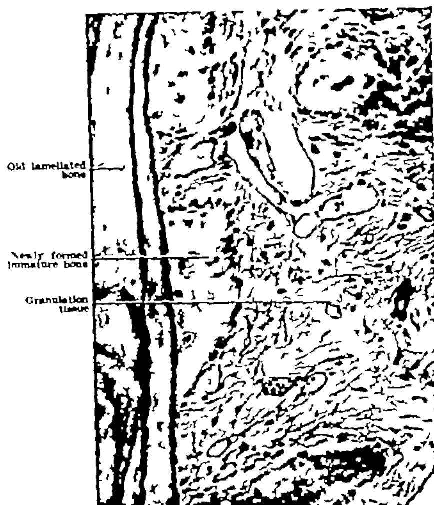


Fig 203.—Detail of section shown in Fig. 202 in high magnification. Note the young richly vascularized connective tissue which has organized the blood clot and the spicules of immature bone rising from the surface of the old lamellated bone. The primitive bone is lined by osteoblasts. (Original magnification X200 reduced to ⅘)

plant, which is brought in contact or remains in contact with living connective tissue A transplant which is still covered by periosteal and endosteal connective tissue, especially if it consists partly of spongy bone has the best chance of survival The circulation of blood in the connective tissue covering the transplant is speedily restored and thus the bone itself may be furnished with the necessary nutrient material sooner than if a covering of connective tissue is absent. Even under the most favorable conditions, the greater part of the

implanted bone tissue will necrotize. The necrosis in itself does not greatly affect or retard healing of the defect. The implanted bone, even if it could be kept vital in its entirety would gradually be replaced by new bone because the structure of the implanted bone is not and can never be functionally adequate

The study of aseptic necrosis has shown that even large areas of necrotic bone are, by a complicated alternation of apposition and resorption, gradually eliminated and replaced by vital bone. In principle, the same process can be observed after a successful transplantation of bone

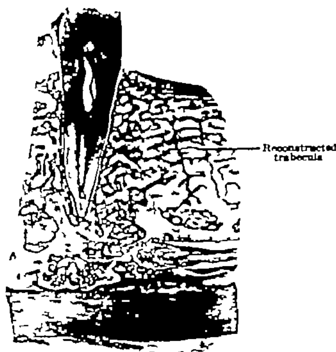


Fig. 201.—Functional reconstruction of the bone in the region of the lower first molar, years after extraction. Twenty four year-old man. Note the horizontal arrangement of the trabeculae. (Magnification X3.)

Successful transplantation can be summarized as incorporation of the graft in the tissues without the development of a severe inflammatory (foreign body) reaction The transplant, parts of which may remain vital, changes the defect in a bone so that it resembles a fracture of a bone. Healing of this pseudofracture may proceed rapidly by the formation of a typical callus at the contact between the graft and the surfaces of the bone defect. Once a bony union between fragments and graft has been accomplished, the function of the repaired bone as a unit has been re-established, and thus a stimulus for gradual functional reconstruction of the graft has been created This process may take many months or even years.

In principle autoplastic, homoplastic, and heteroplastic bone repair follow the same lines. The differences in their success are, in all probability caused by an increasingly severe reaction of the host to the implants.

The filling of a bony defect with some indifferent material containing calcium phosphates has been advocated repeatedly with the implication that these calcium salts would be utilized locally for the formation of new bone. Careful studies have shown that the implanted calcium salts have disappeared when regeneration of bone commences. The beneficial effect of the implantation of calcium salts cannot be denied but the reason for this effect has to be sought along different lines. The stimulus exerted by the implanted foreign bodies leads to the proliferation of young connective tissue cells of which differentiate into foreign body giant cells. It is known that formation of bone can be expected to occur more readily in such young granulation tissue than in the mature connective tissue of a scar which would fill the defect in the absence of an implant. The proliferation of young connective tissue is maintained for a long time by the presence of implanted foreign bodies, a factor which plays a decisive role. Stimulation to tissue proliferation is the most important effect of alloplastic material. It may play also a more or less important role in the other types of bone grafting. The calcium salts and remnants of bone may act, however, also as a stimulus for the differentiation of osteoblasts in the proliferating connective tissue.

The local utilization of implanted calcium salts for the calcification of newly formed bone is as unlikely in alloplasty as it is during healing of bone grafts. The implanted bone is resorbed by osteoclasts which destroy the organic matrix, and the liberated mineral salts are carried away by the lymph and blood and, to some degree but perhaps only under special circumstances, by macrophages. That resorption could increase the local concentration of calcium salts for any length of time seems impossible.

The question of a specific osteogenic potency of the periosteum was often raised in connection with the healing of fractures or the grafting of bone. The many contradictory results of clinical observations and experimental studies can easily be resolved if one recognizes the obvious fact that a specific osteogenic tissue does not exist. All loose connective tissue may, under certain conditions, produce bone (or cartilage). Periosteum per se is not osteogenic if it does not contain osteoblasts or preosteoblasts or if it is not transplanted or maintained in a position or relation in which any loose connective tissue would, by induction, be stimulated to produce bone. The differences in the behavior of periosteum of young growing and of adult fully grown animals after transplantation is one consequence of the presence of osteoblasts in the young and their absence in the older tissue. However, occasionally periosteum taken from adult bones may produce bone. This seemingly contradictory result is caused by the occasional presence of osteoblasts or preosteoblasts in the periosteum of fully grown bones in areas that undergo reparative apposition.

The term preosteoblasts, here used, signifies cells that have already received the inductive stimuli, but have not yet acquired shape, structure, and topographic relations of mature osteoblasts. That the determination of the fate of a cell precedes visible changes in its shape and structure is well documented by the results of experimental embryology.

CHAPTER IX

NECROSIS OF BONE AND INFLAMMATION OF BONES

NECROSIS

Histologic Changes

Necrosis of bone is characterized microscopically by degeneration and final necrosis of the osteocytes (Fig 205) It may be assumed that chemical and physical changes occur also in the intercellular substance but so far clear evidence is lacking Microscopic examination of bones after arterial occlusion shows that not all parts of the bone are necrotized at the same time. Spongy bone and the Haversian lamellae of the compact bone may still be fairly intact, containing undamaged osteocytes. Interstitial lamellae of the compact

bone are the first to become necrotic as shown by the empty lacunae. Sections through such a bone have a peculiar mottled appearance the interstitial lamellae staining darker than the Haversian. In other words the intercellular substance of the necrotic areas of bone betrays its chemical changes by a change in stainability. That in necrosis of bone not only chemical but also physical alterations occur seems to be indicated by the observation of tears in microscopic sections restricted to the necrotic zones and by the separation of necrotic from living bone tissue at the cementing lines.



Fig. 205 — Beginning necrosis of bone. Parts of an Haversian system with many empty lacunae. (Original magnification ×180 reduced to)

Early necrosis of the interstitial lamellae of compact bone was explained by some as a consequence of their reduced metabolism spongy trabeculae and Haversian lamellae being more advantageously situated in regard to the nutrient blood vessels. An alternative explanation is that the interstitial lamellae are damaged first because they represent older parts of the bone tissue than the

haversian lamellae A combination of the two opinions can best explain the greater susceptibility of the interstitial lamellae to injury The interstitial lamellae are remnants of older parts of the bone tissue that have been cut off in some degree from nutrition. As a consequence, after some time they show even in perfectly normal bone some signs of degeneration, then signs of necrobiosis, pyknosis of the nuclei, karyolysis, and, finally signs of disintegration of the osteocytes. Empty lacunae are frequently found in the interstitial

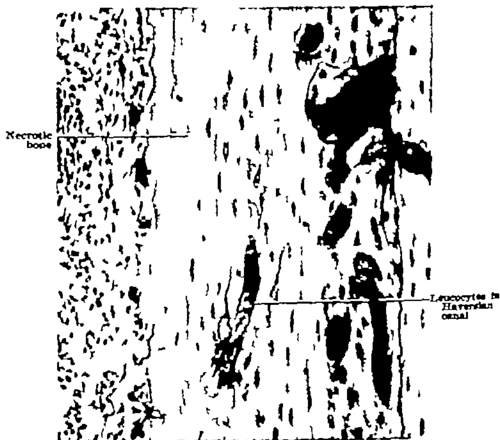


Fig. 10?.—Resorption of necrotic bone. From an infected fracture of the tibia of a rat Not the presence of leucocytes in one of the Haversian canals (Original magnification ×?00 reduced to ?)

lamellae of normal compact bone. An explanation for the diminished resistance of interstitial lamellae should therefore be formulated as follows The interstitial lamellae are older parts of the bone tissue which have already sustained some damage as a result of a decrease in their nutrition prior to the injury which caused the necrosis of bone.

Macroscopically in vivo, or at autopsy the diagnosis of necrosis of bone is difficult. Only the condition of the adjacent tissue, for instance a discoloration and fragility of the bone marrow may point to a necrosis of the bone. Sometimes the periosteum is dry and discolored and can easily be stripped from the bone. Roentgenographically necrotic bone does not differ from living bone. A

roentgenographic or gross anatomic diagnosis of necrosis of bone can be made only in the later stages from the reaction of the surrounding tissue for instance osteosclerosis around necrotic bone or the isolation of necrotic bone by prolifera tion of soft tissues.

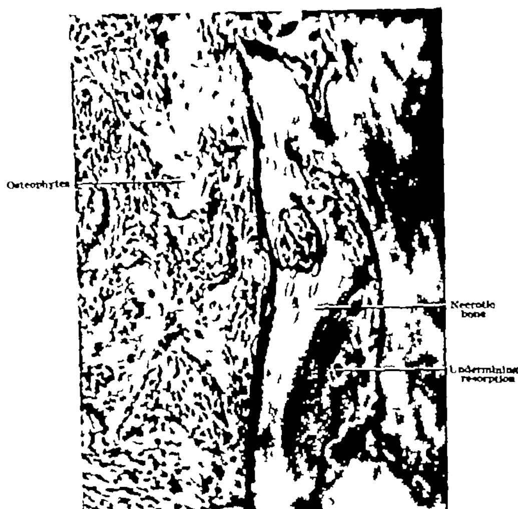


Fig. 207—Apposition of immature bone on the surface of necrotic lamellated bone which at the same time is being removed by undermining resorption. From an infected fracture of the tibia f a rat. (Original magnification ×100 reduced to ⅔)

Fate of Necrotic Bone

The fate of necrotic bone may differ widely The most important single fact is whether the bone is in contact with living reactive connective tissue Biologically speaking the most favorable outcome of necrosis of bone tissue is its elimination by osteoclastic activity (Fig 206) and its gradual replacement by normal living bone This type of healing is frequent and seems to be nothing more than the extension of the regeneration of bone, a process which occurs throughout life. Overaged bone is frequently recognizable in sections by the disappearance of osteocytes, which leaves the lacunae empty In normal re-

generation as well as in the healing of bone the altered state of the intercellular substance seems to furnish the stimulus which induces differentiation of osteoclasts from the cells of the adjacent connective tissue.

If the connective tissue covering one bony surface has been damaged so that it loses its vitality the elimination of necrotic bone is still possible by undermining resorption (Fig 208) which may start in the connective

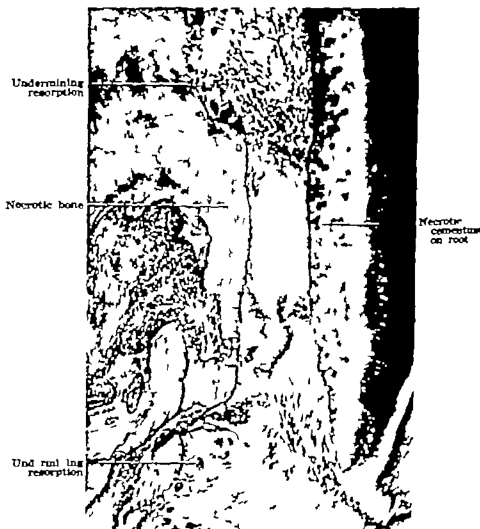


Fig 211.—Pressure necrosis of the alveolar bone caused by exaggerated orthodontic movement of a tooth Undermining resorption starting from marrow spaces and the periodontal membrane outside of the necrotic area. (Courtesy late Dr A. Oppenheim)

tissue of the Haversian canals of compact bone or in the bone marrow spaces after necrosis of the periosteum Similar observations have been made in orthodontic treatment when under too great a force, the periodontal membrane has been destroyed and part of the alveolar bone necrotized. The elimination of this necrotic bone is then achieved by the activity of osteoclasts differentiating from the tissues of the adjacent marrow spaces or even from the periosteal surface of the necrotic bone.

During regeneration of overaged bone the resorption is often *at first incom*te and new bone is built upon the *surface of the partially resorbed bone* (Fig ') In a later phase this new bone and the remnants of the overaged bone may removed but the second phase may be *retarded for months or years.* The same ervation can be made after pathologic necrosis of bone After initial orption the process is reversed before the necrotic bone is entirely eliminated

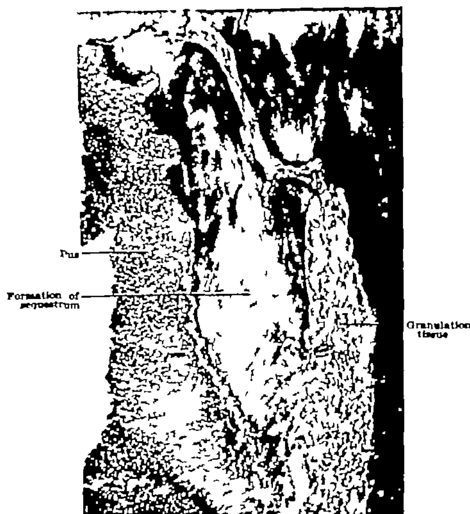


Fig 269 —Formation of a sequestrum in acute osteomyelitis of the mandible. The ecrotic fragment of bone is, for the most part, surrounded by pus. On one surface the ragment is still in contact with reacti connecti e tissue (Original magnification X60; educed to ¾)

This leads to a second and biologically speaking less satisfactory type of healing n bone necrosis. In this case, *resorption plays a minor role and one is tempted* o describe the process as a walling in or burying of the dead bone by increased steoblastic activity New dense, compact bone is formed around the necrotic area, a fact which is especially obvious when spongy bone is transformed into compact bone Excess formation of bone may also occur forming tumorlike

masses which, on the inner surface of compact bone, may narrow or even obliterate the marrow cavity. This type of healing, found in cases of extensive necrosis of bone, may be followed by reconstructive processes which, over a long period, may eventually lead to complete repair.

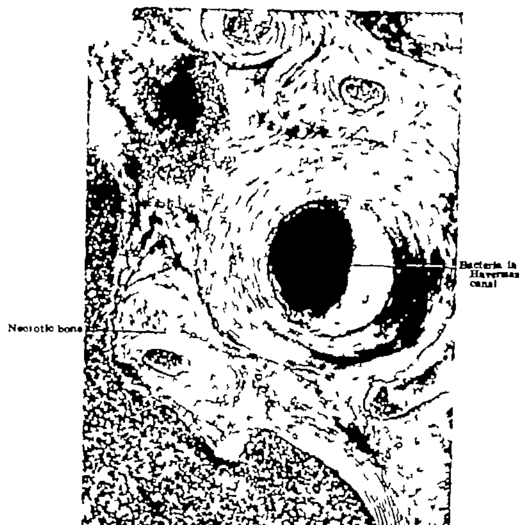


Fig. 210.—Necrotic bone in acute osteomyelitis. Note the presence of bacteria in an enlarged Haversian canal. (Original magnification ×110, reduced 1/3.)

Sequestrum

If necrotic bone loses its connection with living reactive connective tissue, as in suppurative inflammation, its elimination by resorption is impossible. Such an isolated fragment of bone is known as a sequestrum (Figs. 209 and 210). The process which leads to formation of a sequestrum may be a progressive isolation of the necrotic area from the normal bone by osteoclasts, that is, by a process of demarcation. This is made possible only by proliferation of young connective tissue (granulation tissue), cutting off the necrotic from the living bone. If the granulation tissue is then reached by the progressing infection, the necrotic bone may be submerged in pus as a typical sequestrum.

In secondary infection of a fracture isolated fragments of bone may become separated from the living tissue by pus, forming a sequestrum. However it seems that in most cases the demarcation occurs in the necrotic bone at some distance from living bone. Thus the sequestrum is, as a rule, smaller than the necrotic part of bone tissue. The retained necrotic bone is removed by osteoclastic resorption during the phase of healing.

A typical sequestrum after a short time presents a characteristic picture. The surface is irregular and rough and the bone is a yellowish gray and is, of course, freely movable. It should be mentioned that it is often difficult to establish the diagnosis of sequestration in early stages, even if the bone fragment is already movable. A necrotic piece of bone isolated from the living bone by proliferating granulation tissue, is already movable. Some of its surfaces bathed in pus may show a yellowish-gray discoloration and a peculiar roughness, but the granulation tissue may survive and may remain in contact with the deep surfaces. In such cases, the process of sequestration is, to some degree, reversible. Parts of the necrotic bone fragment may become resorbed by the differentiation of osteoclasts from the cells of the granulation tissue. On the other hand, formation of new bone in the granulation tissue on the partly resorbed fragment may even join it to living bone. In the course of this development a process of demarcation may again set in and eliminate a part of the original fragment as a sequestrum.

The elimination of a typical sequestrum may occur by exfoliation through an abscess opening on the surface. In many cases, surgical removal will be necessary. In other instances, the reactive formation of new sclerotic bone around the area of infection and necrosis is extensive and this bone may partly or entirely surround and encapsulate the sequestrated necrotic bone. The formation of such an *involucrum* is especially frequent in chronic inflammation of bone.

Smaller sequestra might be dissolved by the proteolytic action of the enzymes of the purulent fluid surrounding the bone. This dissolution of a sequestrum is comparable to a chemical reaction in vitro rather than to a biologic process.

According to its etiology necrosis of bone can be classified as aseptic and septic. Aseptic necrosis is caused by heat or cold, by metal poisoning, by irradiation or by disturbances of the blood supply of the bone. In the last mentioned category are traumatic and so-called idiopathic bone necrosis. Septic bone necrosis is caused by specific or nonspecific infections. In both cases, the necrosis is a consequence of inflammation caused by the invading organisms. A discussion of the septic necrosis of bone is, therefore, a discussion of the inflammation of bones.

INFLAMMATION OF BONES, OSTEITIS

Classification of Osteitis

The terminology and the classification of inflammatory diseases of the bones are still controversial. An attempt at clarification has to start with the

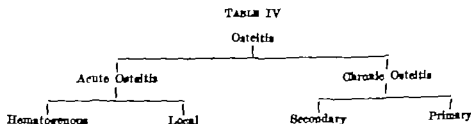
recognized fact that the inflammation of a bone is confined to the connective tissue forming periosteum and marrow and filling the Haversian canals, and that reactions of the bone tissue proper are always secondary. The prefix *osteo* in osteitis, osteomyelitis, and osteoperiostitis relates, therefore, to the bones and not to bone tissue. In this sense osteitis is the general term meaning inflammation of a bone. It implies the involvement of periosteum and bone marrow as parts of the bone as an organ.

A division of osteitis into osteomyelitis and osteoperiostitis seems desirable, although the boundary line between these two diseases is seldom well defined. From a clinical point of view a classification into an acute and a chronic type and, further, according to the etiology is necessary and logical. It is illogical to attempt a classification according to the different reactions of the bone tissue during osteitis and to speak of osteoporotic osteitis, osteosclerotic osteitis, and caries of bone. Osteoporosis and caries are both the result of osteoclastic resorption of bone and differ only in their extent, and to use quantitative differences as a means for classification involves the dangerous implication of qualitative differences as well.

Both osteoclastic and osteoblastic activities are always manifest in inflammation of bones, and the individual cases vary only as one of the processes seems to be more prominent than the other. Even these differences are often only temporary, and to use them for a classification involves the twofold error of describing one phase of a dynamic process as if it were static and of separating two biologically associated processes.

A simple classification of osteitis is given in Table IV.

TABLE IV



Acute Hematogenous Osteitis

Acute hematogenous osteitis presents the classic symptoms of an osteomyelitis. It is a disease of childhood and adolescence. The metastatic infection starts in the marrow spaces of the metaphysis of the growing long bones. As long as these bones grow the capillaries in the metaphysis show a peculiar hair pin shape where the connective tissue invades the calcified cartilage. Retardation of the circulation in these capillaries is, in all probability the reason for bacterial emboli in this area. From here, the infection spreads, in most cases, into the diaphysis and then through Volkmann's canals into and through the cortical compact bone to reach the inner layers of the periosteum. Necrosis and

sequestration of larger parts of the compact cortical layer are the rule with the typical sequelae of sequestration; that is, formation of an involucrum and perforation to the surface through the cloacae

Perforation of the epiphyseal plate involvement of the epiphysis, and finally perforation of the articular cartilage and involvement of the joint are possible, though fairly rare complications.

Acute hematogenous osteitis is, in the majority of cases, caused by the presence of one of the staphylococci most frequently *Staphylococcus aureus*

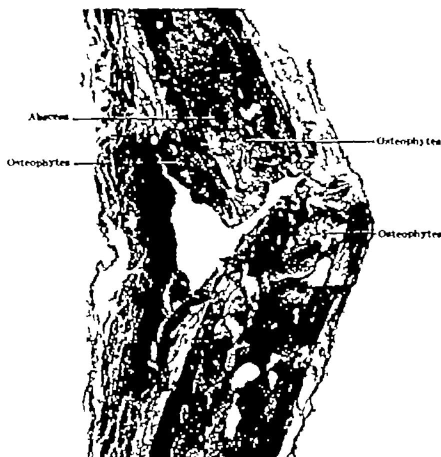


Fig 211 —Acute osteitis in an infected fracture of the rib. General view Note the inflammatory infiltration, abscess formation, and formation of new bone in the marrow cavity and on the periosteal surfaces of the fragments.

Local Acute Osteitis

Local acute osteitis is caused by the infection of a bone or bone fragments from the outside through a wound, as in compound fracture (Figs. 211 and 212) or after tooth extraction (Fig 213) from an infected tooth, or from an infected pneumatic cavity of the skull that is, the paranasal sinuses or middle ear cavities.

Characteristic for all these cases is the more or less rapid and progressive involvement of a bone in an inflammatory process. Resorption of bone, forma

tion of sequestra, and reactive and compensatory formation of new bone are again the three factors in the picture. Their varying combination is responsible for the great variability in the anatomic and the clinical symptoms of the local osteitis.

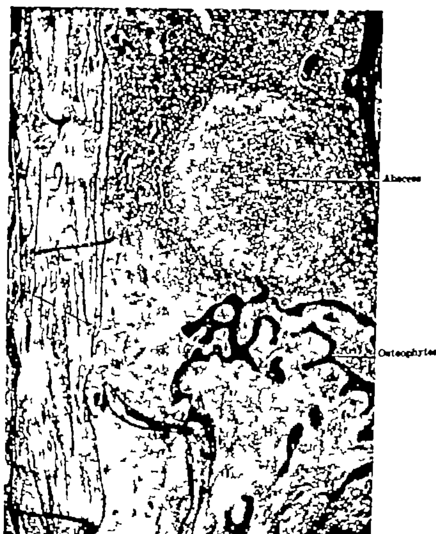


Fig 312.—Detail of the section shown in Fig. 311 Formation of new bone in the marrow cavity in the immediate neighborhood of an abscess.

The reasons for the divergence of individual cases cannot always be determined. Obviously the type and the virulence of the active microorganism are important. A striking example for a different course of bone involvement is the difference between the so-called acute alveolar abscess and acute osteomyelitis, both following the infection of a root canal. In an *alveolar abscess*, it seems that the infection starting in the periapical region of the tooth spreads more or less concentrically involving more and more of the spongy bone. The marrow spaces are infiltrated and the trabeculae are resorbed until the compact plate of the alveolar process is reached. This, too, is resorbed in a

circumscribed area and the inflammation spreads into the soft tissues. In *acute osteomyelitis* of the upper jaw, the infection is first of all much more fulminating than in an alveolar abscess. Moreover there is no concentric enlargement of the involved area but the inflammation extends irregularly over a portion of the jaw involving and destroying for instance the bony socket of the infected and the adjacent teeth. The consequent early loosening of one or more teeth is one of the differential signs. The irregularity of the spread of the infection leads also to multiple erosion of the compact alveolar plate and finally to the establishment of multiple perforations. Formation of sequestra is also characteristic of acute osteomyelitis, whereas it is never observed in an acute alveolar abscess.



A B

Fig. 211.—Osteomyelitis in the anterior region of the mandible of a man fifty-seven years old. Demarcation of a large sequestrum, consisting mainly of spongy bone. Formation of new periosteal bone on the greater part of the outer surface of the mandible and in the granulation tissue at the base of the sequestrum.

A. General view.

B. Higher magnification of an area of the demarcation zone with part of the sequestrum and osteophitic bone.

Secondary Chronic Osteitis

The chronic osteitis is secondary to an acute osteitis. Characteristic is the chronic osteitis in which the inflammation is kept active by a sequestrum that cannot be exfoliated spontaneously because of its size or the involucrum. During the chronic phase of an osteitis, a further expansion of the focus is slow and rare. The reactive formation of new bone is often increased and is sometimes excessive.

Primary Chronic Osteitis

The so-called primary type of chronic osteitis is a chronic inflammation which never did give signs or symptoms of an acute beginning although an acute onset has to be assumed, however short this stage is. It may be divided into simple and granulomatous chronic osteitis. The first is caused by the presence of the common pyogenic bacteria, mostly staphylococci the second, by the tubercle bacillus, *Treponema pallidum Actinomyces bovis* or *Bacillus lepræ*

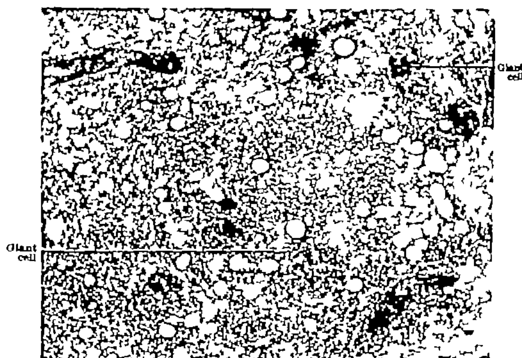


Fig. 214 —Tuberculous osteitis in a vertebra. Note the tuberculous granulation tissue and the giant cells of the Langerhans type. (Original magnification ×110 reduced to ¾)

Simple Chronic Osteitis—Simple chronic osteitis is known as Brodie's abscess. The site of this infection is most frequently the proximal or distal end of the shaft of a long bone The inflammation is self limiting and rarely extends beyond the marrow at the site of its origin, and into the compact cortical bone or through it into the periosteum. Formation of new bone, which is rather extensive, is an early phenomenon. Sclerosis of the bone around the focus of infection does not, we believe *wall off the area of infection. It seems* more likely that early bone production is either a functional response to loss of bone or as some authors believe, a consequence of the low grade infection.

Granulomatous Chronic Osteitis.—

Tuberculous Osteitis.—Tuberculous infection of bones, a disease of the young is a hematogenous infection (Fig 214) involving either the epiphyseal ends of the long bones, especially at the hip knee, or ankle, or the bodies of the vertebrae (Pott's disease) and less frequently other bones. The primary lesion is in the lungs, although often so insignificant that it eludes detection

Pathologically tuberculous osteitis is a more or less rapid destruction of bone often referred to as "caries," which has a tendency to spread into the adjacent soft tissues for example the joints. Reactive or compensatory formation of new bone is, with the exception of long bones, generally not extensive and is overshadowed by the destructive process so that the tuberculous osteitis has often been described as the prototype of rarefying osteitis.



Fig. 216.—Syphilitic osteoperiostitis of the radius. Seven-month-old fetus. Note the excessive formation of new bone in concentri tiers around the necrotic ( ) shaft. (After L. Pick.)

Reparative formation of new bone is characteristic of tuberculous osteitis of long bones for instance, the phalanges, clavicle and mandible. Here destruction of the compact cortical layer from within leads to formation of new bone at the periosteal surface, which is sometimes quite extensive The bones thus afflicted then show a spindle-shaped swelling known as spina ventosa. The fact that this type of tuberculous osteitis is restricted to bones which are under bending or shearing stresses is revealing and can be taken as proof that the formation of new bone is caused by mechanical forces as a compensation for the loss of bony substance and that stimulation by toxins plays, at the best a minor

role. The spina ventosa is, therefore, in all details comparable to the enlargement of bones observed as a consequence of destruction of bone by tumors inside the shaft of a long bone or by giant-cell nodes and cysts.

SYPHILITIC OSTEITIS.—Syphilitic osteitis, whether congenital or acquired, is of two types. The first is the syphilitic gumma, which may develop in the bone itself or may involve the bone by extension from the adjacent soft tissues. The second type is syphilitic osteoperiostitis (Fig 215), a more diffuse infiltration which commences in the periosteum.



Fig. 214.—Actinomycotic osteitis in a vertebra. Colony of the fungus surrounded by inflammatory infiltration. Note the areas of resorption on the bone trabeculae. (Original magnification X110 reduced to ¾.)

Syphilitic osteitis, especially osteoperiostitis, is characterized by extensive formation of new bone. The bones may even be deformed by the superposition of newly formed bone A well known example is the deposition of bone at the anterior surface and crest of the tibia, making this bone appear bent with an anterior convexity (saber shin)

The bone which develops in syphilitic osteoperiostitis, the syphilitic osteophyte, is spongy and of the immature type. It may surround the whole shaft of a long bone in concentric shells connected with one another by radial trabeculae (Fig. 215) The cause of this unusual formation of bone is still controversial. It is seen by some as a reaction to the syphilitic toxin by others, as a response to mechanical stimuli. The latter explanation seems more logical in consideration of the need for emergency repair in syphilitic osteoperiostitis, necessitated by the extensive necrosis of the involved bone.

Although osteoblastic activity is characteristic of syphilitic osteitis, there is l a marked difference between the gummatous and the diffuse syphilitic in nmation of bones. Syphilitic osteoperiostitis leads to a superficial invasion the cortical bone and only the superficial layers are destroyed by osteoclasis. e gumma causes far reaching loss of bone substance in some instances, leading characteristic bone defects Perforations of the palate or nasal septum are nplicated by the destruction of the soft tissues and remain therefore as rmanent defects. Destruction of bone at the bridge of the nose causes the ldleback nose of the syphilitic individual In congenital syphilis the iphyseal growth zone of the long bones is involved. Destruction of cartilage d bone in this area, and its replacement by specific granulation tissue produces e characteristic widening and irregularity of the epiphyseal line and caseous crosis causes its typical yellowish discoloration The destruction in this zone ıds to permanent deformities even if specific therapy is successful.



Fig. 217—Another area of the section shown in Fig. 216. Extensive compensatory forma n of new bone, reinforcing the partly destroyed trabeculae. The newly formed bone is of a coarse fibrillar type. (Original magnification X55; reduced to ⅘.)

Interruption of the regular sequence of layers in the epiphyseal growth me by formation of a layer of granulation tissue presents a characteristic pic ire in the roentgenogram The layer of granulation tissue may either divide e broadened zone of calcification in the cartilage or separate the calcified rtilage from the metaphyseal layer where bone formation occurs around the mnants of the calcified cartilage. Roentgenographically there is not only idening of the zone of calcification, but also division of the zone into two istinct bands, sometimes even into three if the layer of granulation tissue self is doubled.

Actinomycotic Osteitis.—The interplay of destruction and formation of new bone is obvious in actinomycotic osteitis (Figs. 216 and 217) While the destruction of the bone, for example, the mandible, progresses on the interior compensatory apposition of bone occurs at the surfaces causing the sometimes monstrous swelling of the jawbone which gave to the disease the name lumpy jaw

Reaction of Bone in Osteitis

In the confusing variety of symptoms and findings in osteitis, certain basic phenomena merit special attention to clarify the biology of this process.



Fig 218.—Expansion of an acute inflammation into the compact bone. Infiltration of Volkmann and Haversian canals by polymorphonuclear neutrophil leucocytes Beginning degeneration of some osteocytes adjacent to the canals. From an infected fracture of the tibia of a rat. (Original magnification ×100 reduced to ⅘)

The first question concerns the mechanism of bone destruction that is, the causes for osteoclastic resorption of bone (Fig. 218) It seems that there are three factors variously combined in resorption of bone increase of tissue pressure by *the inflammatory exudate toxic necrosis of bone* and the *occlusion of the blood vessels* of the bone The increased pressure which is exerted by the inflammatory exudate on the bone may cause the differentiation of osteoclasts and resorption of bone even before there is visible evidence of necrosis of the bone.

Interference with the blood supply of the bone will also lead to its necrosis. This interference is caused by pressure of the inflammatory exudate on the blood vessels, or by the development of bacterial emboli or by thrombosis.

The infiltration of the bone tissue by toxins, produced by bacteria or resulting from disintegration of body cells, of course leads to necrobiosis of the involved osteocytes. That such necrotic parts of bone are removed by osteoclasis is well known.

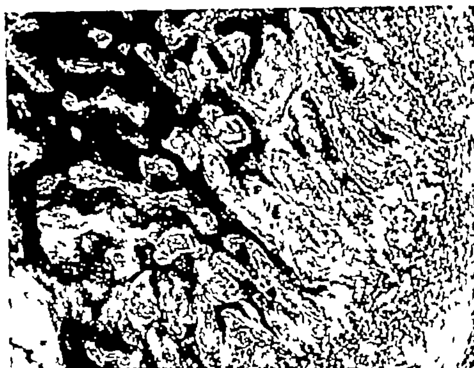


Fig. 219.—Rapid formation of new bone around a focus of osteitis. The bone is of the immature type. The last formed trabeculae are covered with osteoid tissue. The tips of the trabeculae consist of osteoid tissue only. (Original magnification ×120, reduced to [illegible].)

A sequestrum forms when bone tissue loses its contact with living and reacting connective tissue. Necrosis of a part of a bone generally precedes sequestration. That the sequestrum consists almost always of compact bone is generally explained by its low vascularity. This is, of course, not to be interpreted as meaning that compact bone is insufficiently supplied with blood vessels, but rather in the sense that the small number and the arrangement of the Volkmann and Haversian vessels facilitate the interruption of circulation. But there is another aspect of this problem and that is the question as to why necrotic spongy bone is generally removed by resorption and compact bone by sequestration. Resorption is dependent for its effect on the extent of surface area of the bone that is attacked. In relation to the volume the surface area of compact bone is small, even if the Haversian and Volkmann canals are taken into consideration. In spongy bone the relation of volume and surface is reversed in favor of the latter.

A good example of the different behavior *of infected and of* necrotic spongy and compact bone, and thus an example for the *importance of the* spatial arrangement of the bone tissue of the involved bone is the contrast between *maxillary and mandibular* osteitis or osteomyelitis. In the upper jaw there may be *far reaching* destruction of bone by osteoclasts, but sequestra of more than minute size are rarely *found*. In the mandible, sequestration of parts of the heavy compact cortical bone dominates the picture.

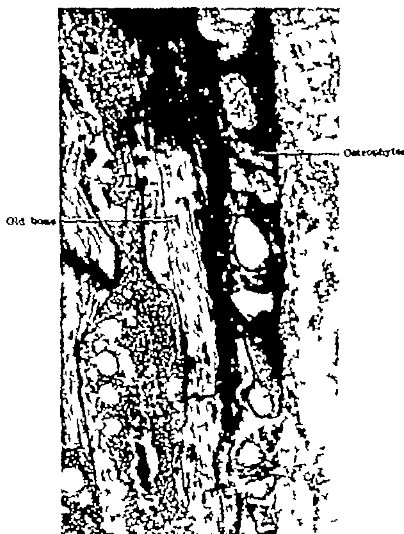


Fig. 220.—Osteophytes on the outer surface of a rib in an infected fracture. Same specimen as shown in Fig. 211. (Original magnification ×120 reduced to ⅗.)

The formation of new bone in and around an area of infection is, according to the opinion of certain investigators due to the stimulating action of toxins at some distance from the focus of infection. Although this contention seems possible, a mechanical factor plays a concomitant, if not dominating, rôle. For this reason, the formation of new bone has been termed compensatory and it is comparable with the osteoblastic activity after fractures and around tumors.

It is the reaction of the supporting tissues to a weakening of the normal bone and an attempt of reinforcement. This response occurs, like many regenerative processes, often in excess, at least in volume. This is especially the case in what is called emergency reinforcements (see page 136). Rapid destruction of bone cannot be compensated for by the rather slow process of apposition of mature lamellated compact bone or even the somewhat faster formation of mature spongy bone. In this emergency spongy bone of the immature type is produced



Fig. 2 1.—Compensatory formation of osteophytes (emergency reinforcement) of a mandible with extens[illegible] osteomyelitis.

forming osteophytes (Figs. 219 to 221). It is well to repeat the statement that osteophytes are not in any way a characteristic feature of bone inflammation, and far less of a certain type of osteitis. Rather the osteophytes are found quite commonly wherever the rate of bone destruction exceeds the maximal rate of production of mature lamellated bone.

Excessive formation of new bone surrounding and containing a sequestrum is known as involucrum. The literal translation of the German term "totenlade"

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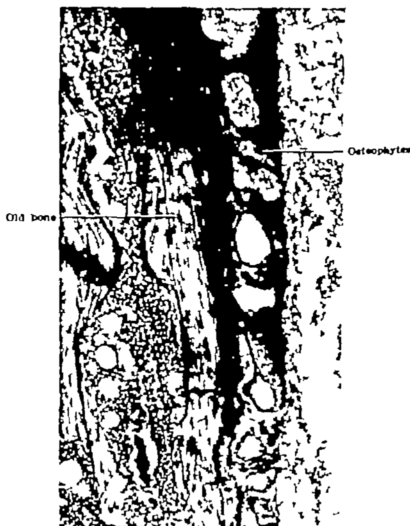


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The formation of new bone in and around an area of infection is, according to the opinion of certain investigators, due to the stimulating action of toxins at some distance from the focus of infection. Although this contention seems possible, a mechanical factor plays a concomitant, if not dominating role. For this reason, the formation of new bone has been termed compensatory and it is comparable with the osteoblastic activity after fractures and around tumors.

It is the reaction of the supporting tissues to a weakening of the normal bone and an attempt of reinforcement. This response occurs like many regenerative processes, often in excess, at least in volume. This is especially the case in what is called emergency reinforcements (see page 176). Rapid destruction of bone cannot be compensated for by the rather slow process of apposition of mature lamellated compact bone or even the somewhat faster formation of mature spongy bone. In this emergency spongy bone of the immature type is produced

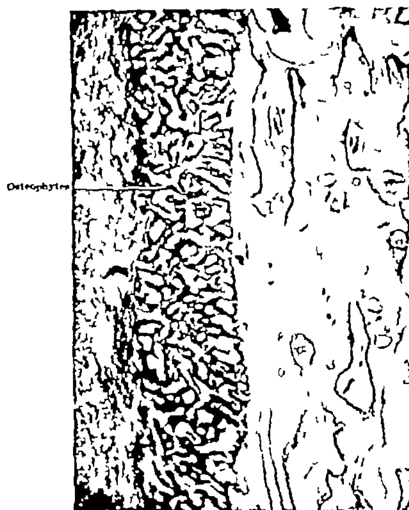


Fig. 221.—Compensatory formation of osteophytes (emergency reinforcement) of a mandible with external osteomyelitis.

forming osteophytes (Figs. 219 to 221). It is well to repeat the statement that osteophytes are not in any way a characteristic feature of bone inflammation, and far less of a certain type of osteitis. Rather the osteophytes are found quite commonly wherever the rate of bone destruction exceeds the maximal rate of production of mature lamellated bone.

Excessive formation of new bone surrounding and containing a *sequestrum* is known as involucrum. The literal translation of the *German term* "totenlade"

namely "coffin," gives an even better picture. The most important cause for the development of an involucrum is the retention of the sequestrum for instance, because of its size, its topographic relations, or the magnitude of osteophytic growth The inflammation is then kept alive and multiple perforation of the involucrum, called cloacae may lead pus to the surface The cavity of the involucrum is always larger than the sequestrum and is lined by granulation tissue that shows signs of chronic or subacute inflammation The development of the involucrum occurs, at least in part by sclerosis and reconstruction of the periosteal and endosteal osteophytes

That the retention of the sequestrum blocking a regeneration at the site of the focus is mainly responsible for the formation of an involucrum is proved by the experience that, as a rule surgical removal of the sequestrum is followed by regenerative formation of new bone

Generalized Hypertrophic Osteoarthropathy

Hypertrophic osteoarthropathy a disease of the skeleton characterized mainly by clubbing of the end phalanges of fingers and toes, an ossifying periostitis of many tubular bones and some mild changes in the joints, is, according to some authors, caused by toxins This disease therefore is logically discussed in connection with inflammatory changes of bones.

While hypertrophic osteoarthropathy especially the clubbing of the digits, was first thought to be a consequence of pulmonary diseases only it is known today that it also follows a variety of other pathologic changes congenital heart disease pyelonephritis, dysentery syphilis, jaundice, biliary cirrhosis, alcoholism and chronic intoxication with phosphorus or arsenic The common denominator of all these pathologic conditions has not been established. Most investigators assume the action of a toxin produced by the primary disease others consider peripheral anoxia, endocrine or neurogenic dysfunction as causative factors. Experimental studies in dogs, that also are affected spontaneously by the disease may lead to an understanding of its pathogenesis.

Clinical Symptoms.—The syndrome occurs in middle life and more frequently in males. The first signs are a thickening of the acral portions of fingers and toes sometimes accompanied by an increase in the curvature of nails. Frequently patients complain of tenderness, pain, and stiffness of the extremities. The periosteal lesions may be recognized in roentgenograms occasionally prior to the recognition of the causative disease. Remission of the symptoms has been observed following the removal of the underlying cause

Pathologic Findings.—The enlargement of fingers and toes is due to hyperemia edema proliferation of loose connective tissue and mild infiltration by lymphocytes and plasma cells. In severe cases the inflammatory changes may lead to pressure atrophy of the bones, more frequently however to spurlike bo[illegible] formation.

In the lo[illegible] bones the changes, usually symmetrical start in the distal third of the [illegible] arm and leg and progress to the proximal ends. In later stages the hu[illegible]us, femur and the shaft of the metacarpal bones may be

affected Lesions have been seen in the clavicle scapula patella iliac crest nasal and malar bones. The insertions of tendons are areas of special predilection

In the long bones, too the lesions start with low grade chronic inflammation of the periosteum The inflamed layer of the periosteum is separated from the cortical bone by the cambium layer that is stimulated to a progressive formation of osteophytes. In the early stages the osteophytic apposition is clearly distinguishable from the underlying compacta In later stages the compacta is resorbed from the surfaces of the Haversian canals and in some instances from the endosteal surface transforming the compacta into spongy bone and in this way eliminating the sharp border between premorbid bone and periosteal osteophytes.

The pathologic changes of the joints are much milder than those in the shaft of the bones. Edema and mild chronic inflammation of the synovia and inner layer of the fibrous articular capsule have been observed

In some cases villous hypertrophy of the synovia and formation of a pannus on the articular surface may occur The subchondral bone trabeculae show signs of resorption Extension of vascularized tufts from the bone marrow through the calcified layer of the articular cartilage may lead to resorption of the articular cartilage itself

PRIMARY HISTIOCYTIC GRANULOMA

The bones are involved in a series of diseases which are believed to be a specific reaction to an infectious agent, the nature of which is not yet known The common feature of these diseases is a tumorlike or diffuse proliferation of histiocytes. The distribution of the nodes can be generalized or more restricted the course can be acute or chronic, malignant or more benign Three diseases are believed to be of the same principal type namely Letterer-Siwe s disease Hand-Schüller-Christian s disease and the eosinophilic granuloma.

The severity of these diseases seems to be correlated to some measure to the age in which they occur The severity is not only expressed in the acute course with its fatal outcome but also in the much wider distribution of the lesions

The organs which are most commonly involved are those which contain normally a greater amount of histiocytes or macrophages. These organs are the lymph nodes and lymphatic follicles, the spleen the thymus, the tonsils, the liver the skin and the bone marrow Diffuse accumulations of histiocytes are also found in the connective tissue of the lungs and heart and in some endocrine glands. It is interesting to know that the involvement of the bone marrow and therefore the skeleton is common to all the three types of those diseases of the macrophage or reticulo-endothelial system

Letterer-Siwe s Disease

Letterer-Siwe s disease affects infants and children below the age of two years, runs an acute or sometimes subacute course and ends fatally in weeks

or months. Only rarely does the disease last for one or two years. Clinically the disease is characterized by enlargement of the liver of the spleen, and of the lymph nodes and by the appearance of distinctive lesions in the bone. The skull is most often affected.

Hand-Schüller-Christian's Disease

Hand-Schüller Christian's disease is a disease of later childhood, starting in many cases between the ages of five and ten years. The onset of the disease however may occur much later even in the twenties or thirties. The lesions are most frequently found in the bones of the cranial base especially in the optic and hypophyseal regions and in the bones of the calvaria. The lesions are responsible for the so-called Hand-Schüller-Christian triad of symptoms exophthalmus, diabetes insipidus, and circumscript defects in the cranial vault. Exophthalmus is caused by the expansion of a node into the orbit diabetes insipidus by involvement of the hypophysis and hypothalamus. The classic triad is often enough not complete and, in many cases, involvement of other organs leads to more conspicuous symptoms. Early degeneration of the hypophysis may lead to dwarfism and hypogonadism. The first signs of the disease may appear in the jaws as cystic defects. The growth of the nodes may lead to loosening and loss of teeth. Any other bone of the skeleton may be the site of the histiocytic proliferation, especially the humerus and femur of other organs the lymph glands, spleen liver skin, and, most frequently the lung may be involved. The course of Hand-Schüller-Christian's disease is chronic, extending over a period of ten to fifteen years, and is fatal by secondary involvement of the hypothalamus or of the heart in pulmonary location of the lesions.

Eosinophilic Granuloma

The eosinophilic granuloma affects the skeleton only arising in the marrow of one, or of a few or in some cases, of many bones. The bones of the calvaria, ribs, vertebra, humerus femur and mandible are the most frequent sites of the eosinophilic granuloma. The eosinophilic granuloma can be considered as a benign disease of the skeleton which may heal spontaneously or after simple exochleation of the granulation tissue. The presence of eosinophilic cells is thought to indicate an allergic origin or reaction.

The characteristic cellular elements of Letterer-Siwe's disease Hand-Schüller-Christian's disease, and the eosinophilic granuloma are the histiocytes or macrophages, derivatives, in all probability of reticular cells or the resting wandering cells of the loose connective tissue. The cells are large irregular polyhedral with a large nucleus which is often irregular in shape. The presence of two or even more nuclei in one cell is not rare. According to their phagocytic quality particulate matter is often found in the histiocytes for example fragments of red blood corpuscles or after their digestion, hemosiderin.

Whereas lymphocytes and plasma cells appear here and there in the histiocytic nodes, the presence of great numbers of eosinophilic cells is characteristic for the eosinophilic granuloma. These cells often have an appearance identical to that of eosinophilic leucocytes with their bilobed nucleus. Other cells have a compact, sometimes indented nucleus. Their cytoplasm is filled with bright, coarse eosinophilic granules (Figs. 222 and 223).



Fig. 222.—Eosinophilic granuloma. Note the large histiocytes, characterized by their pale nuclei, and the smaller eosinophil leucocytes characterized by their polymorphous darkly stained nuclei. (Original magnification ×400, reduced t) (Specimen, courtesy Dr. M. B. Alsenberg.)

Letterer-Siwe's disease seems to be an acute and more generalized, Hand-Schüller-Christian's disease a chronic and more localized type of the same lesion. Their close relation is made probable by the observation that the lipidization and the scarring which are so characteristic for Hand-Schüller-Christian's disease have also been found in the rare instances of subacute Letterer-Siwe's disease after duration of one to two years. The lipidization is caused by the phagocytosis of cholesterin by the histiocytes which then assume a more or less typical appearance of foam cells or xanthoma cells. The

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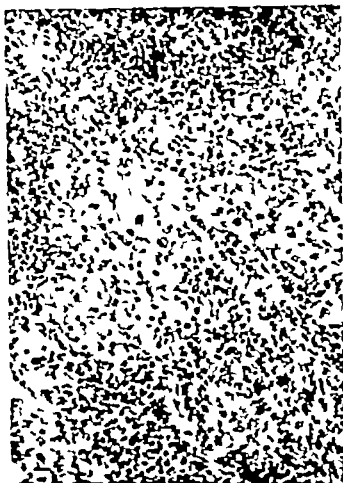


Fig —Eosinophilic granuloma. Note the large histiocytes characterized by their pale nuclei, and the smaller eosinophil leucocytes characterized by their polymorphous darkly stained nuclei. (Original magnification ×400 reduced to) (Specimen, courtesy Dr M. S. Altenberg.)

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collagenization of the scarring of nodes in Hand-Schüller-Christian's disease seems to be a consequence of rather extensive necrosis and can be considered as a process of repair

The relation of the eosinophilic granuloma to the other two types of histiocytic proliferation has been established by the presence of great numbers of eosinophilic cells in one of the nodes of an otherwise typical case of Letterer Siwe's disease. It was mentioned that the presence of eosinophils may be due to an allergic factor The fact that the eosinophilic granuloma is the most restricted type of histiocytosis and at the same time its most benign expression may be correlated to the fact that allergy is somehow related to immunity

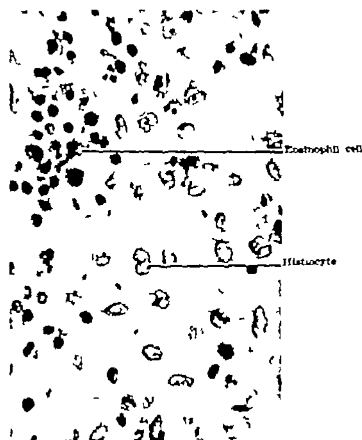


Fig. 223 —Eosinophilic granuloma. Eosinophil cells between histiocytes. (Magnification X750.) (Specimen, courtesy Dr A. B. Ragins.)

The skeletal lesions of the different types of histiocytosis arise from the reticular cells of the bone marrow The surrounding bone reacts to the tumor like growth of the nodes by being resorbed so that typical areas of rarefaction develop A concomitant and compensating formation of new bone can also be observed. In the jaws, foci of Hand-Schüller Christian's disease have often been diagnosed as radicular or follicular cysts. The involved bones may be the site of spontaneous fractures

Gaucher's Disease

Osseous xanthomas are characteristic for Gaucher's disease. It is thought that this disease is caused by a disturbance of the cellular fat metabolism in the macrophage system. The reticular cells and histiocytes in liver, spleen,

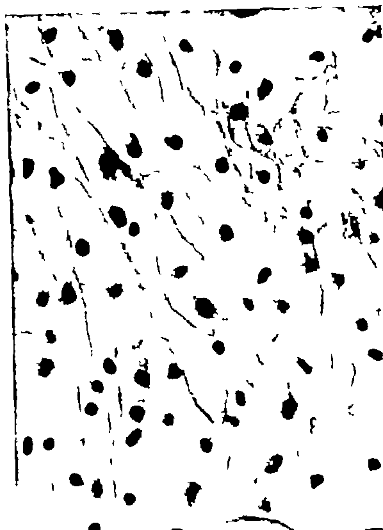


Fig. 224.—Gaucher's disease. Typical xanthoma cells. (Original magnification ×1000, reduced to [illegible].)

lymph nodes, and bone marrow accumulate great quantities of kerasin, a cerebroside, and change into typical xanthoma cells or *foam cells* (Fig. 224). The disturbance of the cellular activity leads to extensive proliferation of the histiocytes and to the development of tumorlike masses. In the skeleton, large defects of the bones, accompanied by compensatory growth of bone, are found. The proliferating cells seem to undergo frequently degenerative and necrotic changes. In spongy bone where many marrow spaces are filled with strands of Gaucher's

cells, necrosis of these cells leads also to more or less extensive necrosis of bone trabeculae. Hyalinization of the necrotic tissue and consecutive scarring or calcification are not infrequently observed (Fig 225)

Gaucher s nodes may be found in all bones of the skeleton. The bones most often involved are the femur sternum, and vertebrae.

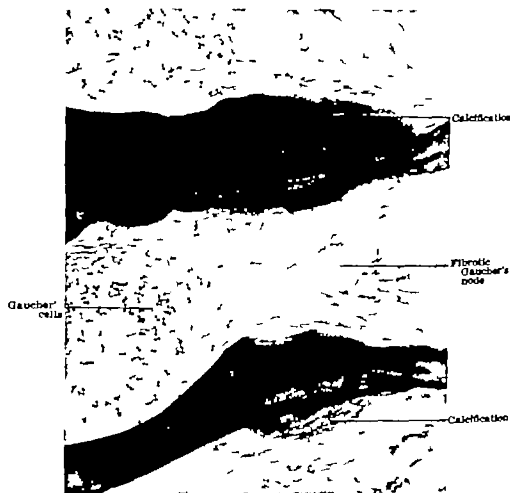


Fig 225—Gaucher' disease. Necrosis, hyalinization, and localized calcification of the Gaucher cells. The bone of the trabeculae is, in part, necrotic.

Niemann Pick s Disease

Another type of lipidosis characteristic for early infancy is Niemann-Pick s disease characterized by the presence of sphingomyelin in the histiocytes. Skeletal lesions in this malignant disease are rare.

ASEPTIC NECROSIS OF BONE, OSTEOSIS

Classification

The aseptic rosis of bone, whether from known or idiopathic causes, is a regressive or d nerative process. We suggest osteosis as a collective term

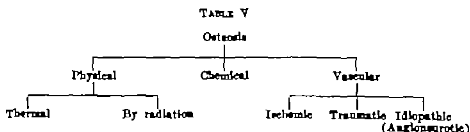
for all these pathologic changes. We are aware that the use of the term osteosis to signify all the noninflammatory degenerative bone changes does not conform with the definition of the suffix *osis* as ' signifying a condition of or state caused by (Gould) but medical and dental usage tends to differentiate between the suffixes *itis* and *osis*. Nephritis, for example is the inflammation of the kidney; nephrosis, a noninflammatory (degenerative) disease of this organ Periodontitis is the inflammation of the periodontal membrane; periodontosis, its noninflammatory destruction

The reaction of bone tissue in aseptic necrosis is not different from that observed in inflammation of a bone We can observe again the interplay of osteoclasis and formation of new bone. In individual cases, one or the other of these biologically integrated processes may temporarily dominate the clinical or the histologic picture. Resorption of greater portions of necrotic bone frequently entails an intensive proliferation of young connective tissue and with it the formation of numerous new blood vessels. If the process of regeneration resorption, and formation of bone proceeds undisturbed, complete healing of an osteosis may be observed. Mechanical injuries or secondary infection occurring during this period frequently complicate the process of healing so that an osteosis ends with permanent deformity of the involved bone.

The secondary infection may occur from invasion of bacteria from the surface as, for instance, in primarily aseptic necrosis of the jaw the infection may be hematogenous, bacteria settling in the necrotic area, which has lost its power of resistance. In secondary infection aseptic necrosis is changed to septic necrosis, and the osteosis becomes an osteitis.

According to its etiology osteosis can be classified as shown in Table V

TABLE V



Thermal Osteosis

In gangrene of an extremity from burning or freezing, the involved skeletal parts are, of course found to be necrotic. The necrotic parts are demarcated and separated from the intact parts of the bone by osteoclasis and proliferation of granulation tissue. Experiments have shown that bone has less resistance to low temperatures than does soft tissue. Extensive necrosis of bone can be observed after freezing of an extremity while muscles, vessels, nerves, and skin remain intact. In experiments, epiphyseal cartilage is found to be necrotic, while articular cartilage remains alive. The difference in resistance of epiphyseal and articular cartilage is found in other types of osteosis and can be explained by their different sources of nutrition. Articular cartilage is

nourished by fluid diffused from the synovial fluid. Injury to or necrosis of, the bone marrow will therefore diminish or interrupt the flow of nutritive elements to the epiphyseal cartilage whereas the nutrition of articular cartilage is not interfered with.

Radiation Osteosis

Necrosis of bone from an overdosage of roentgen or radium rays is well recognized. Because of its ready absorption of these rays, bone may already have been destroyed at a time when the soft tissues covering the bone are still intact. This greater susceptibility of bone to irradiation is important in determining dosage in roentgen or radium therapy. A special case of bone necrosis from contact with radioactive substances is observed in factories using luminous paint for instance, for dials of watches. Workers in such factories at one time suffered from extensive necrosis especially of the jawbones. These aseptic areas of necrosis were regularly infected by bacteria from the oral cavity or from infected teeth. It is because of the chronicity of the osteosis resulting from contact with radioactive particles that the victims frequently show extensive reparatory or compensatory formation of new bone.

Chemical Osteosis

Chemical osteosis is today a rarity. It was formerly observed mainly in dentistry after the application of arsenic and in factories employing phosphorus in the manufacture of matches. The use of arsenic has been largely discontinued by the dental profession and the use of yellow phosphorus in factories is unlawful in most countries.

The arsenic necrosis in most instances involved parts of the interdental septum if after the application of arsenic the cavity was not hermetically sealed. In most instances, secondary infection from the oral cavity complicated the primarily aseptic necrosis.

Phosphorus necrosis almost invariably involved the jawbones. Frequently necrosis of the entire lower jaw occurred accompanied by extensive production of new bone as an involucrum around the sequestrated mandible. Here also, secondary infection was the rule.

Ischemic Osteosis

Occlusion of blood vessels, for instance by an embolus, in arteriosclerosis, or by nitrogen bubbles in the bends (caisson disease) will, of course lead to more or less extensive necrosis of those bones which are deprived of their blood supply. The limitation of the necrosis will depend on a possible collateral circulation. *Conditions are generally speaking unfavorable* for the establishment of a collateral circulation. The arteries which supply a bone are with the exception of the nutrient arteries, quite small though numerous. This arrangement of blood vessels is characterized by the presence of many narrow and therefore not very efficient, anastomoses.

Traumatic Osteosis

Trauma leads to necrosis of bone if it destroys or greatly restricts the blood supply of the bone. Therefore necrosis of smaller or larger areas of bone is a common finding after fractures, which of course causes the rupture of many blood vessels. Apart from the necrosis of isolated fragments of bone, the extent of necrosis of parts of the main fragments of fractured bone depends on the relation of the fracture to the blood vessels supplying the bone. In all bones in the adult, injury to the nutrient artery or to one of its branches may lead to necrosis of larger areas of the bone marrow and secondarily to necrosis of adjacent spongy or compact bone. Fractures in the metaphyseal region are more favorably situated as to nutrition because of the blood supply to the metaphysis and epiphysis from the nutrient artery on one side and from arteries entering through the articular capsule and ligaments on the other

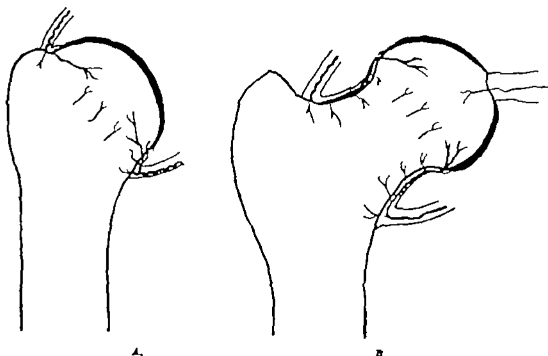


Fig. 224.—Diagrammatic longitudinal sections through humerus, *A* and femur *B* with attached capsule The branches of the capsula arteries supplying the head of the humerus enter from the attachment f the capsule directly The branches of capsula arteries supplying the hea l of the fem hav to run the entire length of the neck of the femur to reach the head from the attachment f the capsule

In fractures of the hip in the adult, the head of the femur frequently undergoes necrosis. Explanations vary but many observers believe that the blood supply to the femur head is primarily scanty This theory seems entirely unfounded when it is realized that the structure and the function of the femur head and neck are at least equal to those of spongy bone in other parts of the skeleton. Other observers consider the intracapsular location of the fracture as responsible for interruption of the blood supply since the capsular arteries play the most important role in nourishment of the femur head.

Branches of the nutrient and metaphyseal arteries extending into the head after the ossification of epiphyseal cartilage are second in importance. The arteries which enter the head of the femur through the ligamentum teres, though of major importance during the growth period, are, in the adult, of only negligible significance and may sometimes even be obliterated.

The importance of the intracapsular location of the fracture of the neck of the femur becomes clear if longitudinal sections through the humerus and femur and through the articular capsule are compared (see Fig 226) The synovial capsule commencing at the edge of the articular cartilage covers, in the shoulder joint, only a narrow strip of bone, the anatomic neck. Here, the capsule is fused with the periosteum. In contrast to this relation of capsule to humerus, the area of the femur covered by synovial membrane, and therefore intracapsular is extensive. The synovial capsule covers virtually the entire neck before it is reflected away from the bone to line the inner surface of the fibrous capsule.

To reach the head of the humerus, the branches of the capsular arteries have only to traverse the narrow zone in which the synovial capsule is attached at the anatomic neck. In the femur the blood vessels have to run almost the entire length of the neck, from the point where the fibrous and synovial capsule are attached to the bone to the point where the synovial capsule ends in contact with the articular cartilage. Thus, the arteries supplying the head of the femur are exposed to injury much more commonly than are those of the head of the humerus and other articular extremities. Moreover the chance that some of these arteries may escape injury is slight.

Idiopathic Osteosis

A number of bone necroses, characterized by their specific location, have been identified as spontaneous or idiopathic. Although their principal pathologic identity has been recognized by most observers, they are still described under separate names which to make matters worse, are mostly derived from the first describer of the specific manifestations of the disease. Doubts as to priority are kept alive by the selection of different proper names in different countries. Such terms as Köhler's diseases (he described two types of idiopathic necrosis of bone) Freiberg's disease, Perthes or Legg Calvé's, or Legg Calvé-Perthes disease, Kienböck's disease and Osgood-Schlatter's disease may have contributed to the prestige of the author but they confuse the student and prevent the understanding of the unity of all these diseases as different manifestations of a pathologic entity The use of proper names in the designation of pathologic processes should be abolished, or these names should be placed in parentheses after the scientific terms. *We suggest idiopathic osteosis as the* collective term and the name of the specific bone to designate the location characteristic of an individual case Then Legg-Calvé Perthes disease becomes the idiopathic osteosis of the femur head (Legg-Calvé-Perthes) (Fig 227) Freiberg's disease is the idiopathic osteosis of the second metatarsal head (Freiberg) (Fig 228) Köhler's disease, the idiopathic osteosis of the tarsal navicular bone (Köhler)



A



B



C



D

Fig 227.—Idiopathic osteosis of the femur head. (After G. Axhausen and E. Bergmann.)
A At the start of the disease. Epiphysis irregularly outlined.
B Six weeks later. Epiphysis flattened.
C Six months late. Increased flattening of epiphysis.
D Healing after two and one-half years. Epiphysis quite flat and fused to neck of femur

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D

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(Fig 229 A) Kienbock's disease the idiopathic osteosis of the os lunatum (Kienbock) (Fig 229 B) and Osgood-Schlatter's disease, the idiopathic osteosis of the tuberosity of the tibia (Osgood-Schlatter) The use of the broader term idiopathic osteosis in all these instances is the more justified because the necrosis of sesamoid bones, of vertebral bodies (Fig 230) and of bones in the skull, and the so-called osteochondritis dissecans (Fig 231) are manifestations of the same pathologic entity differences in the anatomic picture being due entirely to the specific sites

Idiopathic osteosis is a disease of childhood and adolescence, especially if the epiphyses are involved. In other sites, in the carpal or metatarsal bones, for instance, it often occurs in later years (in the twenties or thirties)

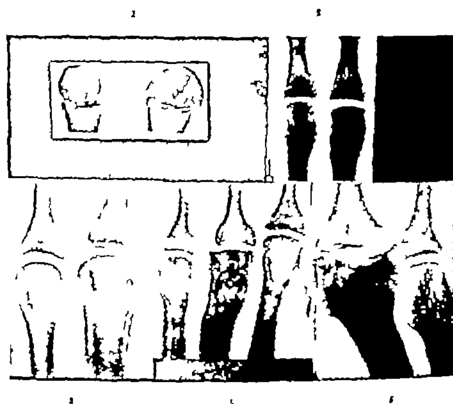


Fig 228.—Five consecutive stages of idiopathic osteosis of the metatarsal head. (After G. Axhausen and E. Bergmann.)

For some of these different variations of idiopathic osteosis, a sequence of highly characteristic stages has been worked out It is safe to assume that this development is in its broad outlines, valid for the entire group

The early stage is characterized by total necrosis of bone tissue and marrow of an epiphysis or part of it or of a bone or part of it Macroscopically and roentgenographically no changes can be seen at this time. It must be stressed that there is no fracture, infraction or epiphysiolysis. Neither is any rupture or any other damage of blood vessels evident. The articular cartilage is found



A B

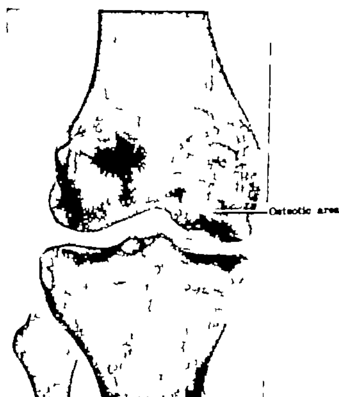
Fig. 229.—*A*. Idiopathic osteosis of the tarsal navicular bone.
B. Idiopathic osteosis of the carpal lunatum.
(After G. Axhausen and E. Bergmann.)



Fig. 230.—Idiopathic osteosis of the twelfth thoracic vertebra. (After Löhr.)



A.



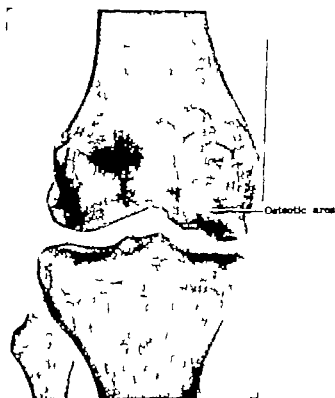
B

Fig. 231 — A Idiopathic osteosis of the capitulum of the humerus. B Idiopathic osteosis of the medial condyle of the femur (After G Axhausen and E. Bergmann.)





A

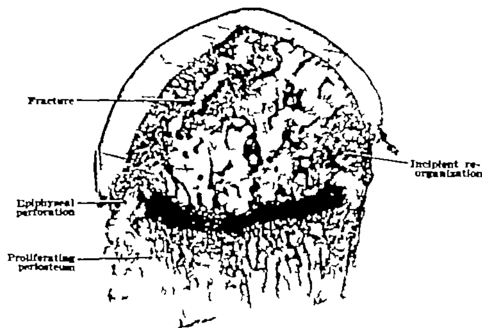


B

Fig 231 — *A* Idiopathic osteosis of the capitulum of the humerus. *B* Idiopathic osteosis of the medial condyle of the femur (After G Axhausen and D. Bergmann.)

act not only by macroscopic but also by histologic examination. It has been nted out that the resistance of articular cartilage to vascular injury is due to fact that this cartilage is nourished by the articular synovial fluid. It is refore independent of the blood vessels of the bone

The next stage is repair During resorption of the necrotic bone young nnective tissue invades the involved area and new bone is substituted for crotic bone. Frequently some trabeculae escape resorption partly or entirely d new bone is laid down on their surface The newly formed bone is of the mature coarse fibrillar type At the same time the necrotic marrow is placed by granulation tissue after the cell debris has been removed by acrophages.



g 232—Necrosis of the metatarsal head with impression fracture. Incipient reorganization of the necrotic area. (After O Axhausen and E. Bergmann.)

The regenerative process may if undisturbed, achieve complete healing it healing seems to be the exception rather than the rule. The necrotic bone, hich has lost its normal resistance to mechanical stress, is often subjected spontaneous or pathologic fractures (Fig 232) The fracture always traverses e necrotic area and does not occur between living and dead bone. During frac ures, the articular cartilage is damaged because it has lost the firm support hich the normal bone gave. This is the stage when idiopathic osteosis is evident roentgenograms. The impossibility of seeing any changes prior to secondary athologic fracture has led to the misconception of traumatic breaks in the ontinuity of the involved bone as the cause of the necrosis.

Specific consequences arise from the fact that the fracture is bounded by ecrotic bone on both sides. Continued friction between the two fragments

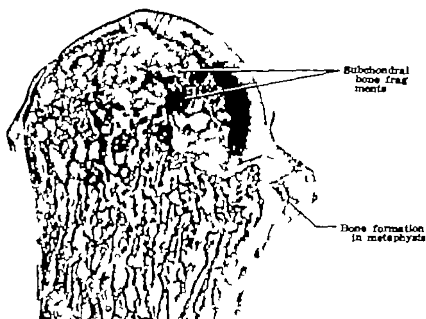


Fig. 233.—Demarcation and reorganization in metatarsal osteosis. (After G. Axhausen and E. Bergmann.)

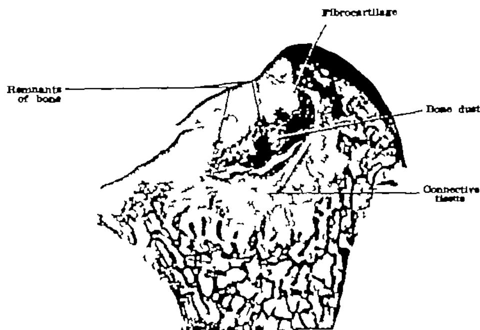


Fig. 234.—Later stage in the demarcation and elimination of the necrotic bone in metatarsal osteosis. (After G. Axhausen and E. Bergmann.)

causes a grinding of the necrotic bone and the zone of fracture is soon filled with bone dust, which is forced into the neighboring bone plugging the marrow spaces. Thus an area of density is created and one part of the necrotic bone is then separated from the other by a barrier which offers great resistance to resorption and especially to regeneration of the peripheral walled-off bone. While regeneration of the proximal zone continues, the barrier itself is gradually removed, being replaced by a layer of young connective tissue. A separation has taken place between the regenerated and the necrotic part of the damaged area. The stage is clearly visible in the roentgenogram (Figs. 233 and 234).

The fate of the demarcated area, which is, to a greater or less extent covered by the damaged articular cartilage is not predictable. It may be invaded by granulation tissue and be partly or in favorable cases, entirely regenerated, although the deformities caused by the spontaneous fracture or fractures are permanent. The necrotic fragment may even unite with the regenerated fragment. In other cases, the regeneration is only partial or is lacking. Union of the fragments may not occur regardless of whether or not the distal fragment underwent regeneration. A permanent division of the involved bone has not infrequently been observed in carpal, tarsal, and sesamoid bones. In those instances in which smaller parts of articular condyle or head of a bone necrotize (osteochondritis dissecans) the nonunion of the necrotic fragment and the rest of the bone may lead to the formation of free articular bodies.

Necrotic parts of bone may after an initial stage of greater radiolucency due to osteoclasis, enter a stage of greater radiopacity from impregnation of the necrotic tissues with calcium salts.

The ischemic origin of idiopathic osteosis is generally conceded. The details of the mechanism are still in doubt. Direct injury of blood vessels by a trauma whether it is remembered by the patient or not, cannot be excluded in all cases but seems to be of minor importance.

Observers tend more and more to regard repeated minor traumas as the cause of ischemic necrosis of a bone or part of a bone. Experiments showing that a single application of a tourniquet may be harmless, but repeated application injurious, are quoted as proof. It is illogical to regard the single trauma as not causing *any* damage. Repetition of a trauma can lead to severe disturbances only by a summation of damages. In other words, the first or a single trauma must have some effect which is reversible if the restitution is not disturbed. If however the trauma is repeated before the effects caused by the first incident have disappeared the residual damage will be accentuated, and in due course severe injuries will ensue.

An increasing vascular damage during the time of repeated trauma must be assumed even though microscopic examination does not reveal any morphologic changes of blood vessels in and around the involved area of a bone. Only one vascular disturbance could lead to ischemia without being detectable morphologically namely a neurovascular injury.

The development of idiopathic osteosis as a mechanically caused, increasing neurovascular unbalance, leading to an ischemic necrosis, must be visualized.

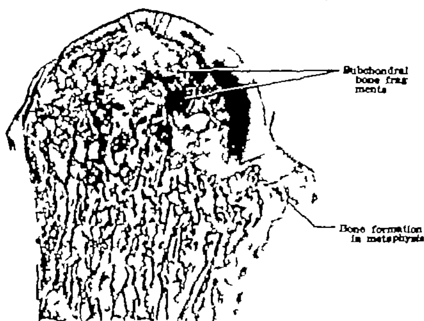


Fig 233.—Demarcation and reorganization in metatarsal osteosis. (After G Axhausen and II. Bergmann.)

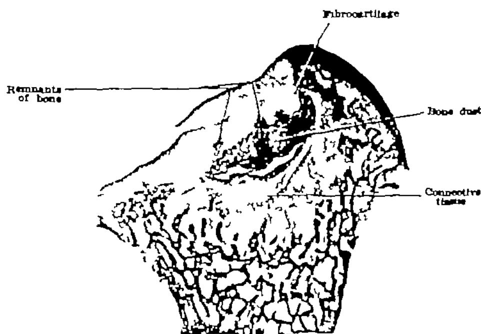


Fig 234.—Later stage in the demarcation and elimination of the necrotic bone in metatarsal osteosis. (After G. Axhausen and II. Bergmann.)

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The development of idiopathic osteosis as a mechanically caused, increasing neurovascular unbalance, leading to an ischemic necrosis, must be visualized.

The mechanical factors may be external for example, use of a pneumatic hammer or chisel in osteosis of the os lunatum or they may be internal for example, abnormal tension of tendons, ligaments, or the articular capsule, through which blood vessels enter the bone.

The question has repeatedly been asked how regenerative processes can take place in spite of persistence of the mechanical noxae which had primarily disrupted the normal blood supply of the involved area. The explanation of this paradox is that the regeneration initiated by proliferation of granulation tissue involves the formation of numerous new blood vessels which enter the bone in areas outside the danger zone. In fact, the regenerative, proliferative activity can be regarded as indirect proof of localized vascular damage.

From the analysis of vascular damage causing idiopathic osteosis, the provisional term *angioneurotic osteosis* is suggested.

CHAPTER X

TUMORS OF THE SKELETON

DEFINITION

A tumor is an independent or autonomous overgrowth of a tissue which does not serve a useful purpose. By the use of the term independent or autonomous, the tumor is characterized as being outside the genetic pattern of the individual and out of balance with the other tissues. A tumor fulfills no useful purpose in contradistinction to proliferative tissue which serves the defense of the body for example, proliferative tissue (granulation tissue) that develops during inflammation or during regeneration.

Tumors are either benign or malignant. Benign tumors are characterized by a marked differentiation of their elements, which, in most cases, resemble the mother tissue. They show a moderate rate of growth and grow by expansion dislocating and compressing the neighboring tissues and organs. They may be multiple, but they do not produce metastatic lesions by dissemination of their elements. A benign tumor therefore, does not kill its host directly but can become fatal by compressing vital organs (brain)

A malignant tumor is generally characterized by cells of lower differentiation than those of the mother tissue. It grows fairly rapidly by invasion of the surrounding tissues and organs. It has, therefore, a tendency to invade the blood or lymph vessels and elements of the tumor may be carried to remote regions of the body and give rise to metastatic growth. The histologic differential

diagnosis between benign and malignant tumors is often extremely difficult. The only decisive factor in diagnosing malignancy is the observation of invasive growth of the tumor cells.

As yet we have no full understanding of the causes of tumors, although some tumors are evidently caused by chronic mechanical or chemical irritation while others seem to result from an inherited tendency. The level of differentiation of tumor cells as compared with that of the mother tissue helps to determine the degree of malignancy of a tumor. The lower the differentiation of the tumor cells, the more malignant the tumor.

ANAPLASIA

The fact that tumor cells are "dedifferentiated" has been called by some anaplasia. It has been explained by the assumption that some cells of the tissue may have remained in an undifferentiated embryonic state. No fact is known that would substantiate this hypothesis. It is, of course, necessary to distinguish sharply between islands of *embryonic cells* in a tissue which has otherwise undergone normal differentiation and the remnants of *embryonic organs* or structures which, in the normal course of development, disappear. Whereas the existence of the former is not only entirely hypothetical but also highly improbable, many examples can be cited of the existence of the latter as foci of tumors. It is inconceivable that remnants of the primary perichondrium of a long bone could survive to the period of regular bone formation and should form an island of embryonic perichondrium in the adult periosteum. On the other hand, remnants of the notochord may give rise to chordoma, and remnants of branchial pouches may develop into cysts or occasionally a carcinoma.

In many cases, young tissue, for instance, connective tissue, has been erroneously identified as embryonic connective tissue. Wherever proliferation of connective tissue occurs, as, for instance, in inflammation or during healing of wounds, the newly formed young connective tissue is richer in cells and capillaries and poorer in fibrous elements than is the mature old connective tissue. Still it is widely different from embryonic connective tissue or mesenchyme. Wherever cartilage grows by differentiation from connective tissue, the youngest layers of cartilage are characterized by the preponderance of cells over intercellular substance and by the small size of the cells. It is entirely incorrect to identify this tissue with embryonic precartilaginous tissue.

An added difficulty is presented by the efforts of many investigators to identify each variety of tumor tissue with a type of normal tissue, which is possible only within certain limits. The tissues of a tumor are the product of pathologically proliferating and differentiating cells and may, therefore, be aberrant variants of a normal tissue which are never seen in normal development. The tissue of a myxoma is similar to mucoid connective tissue but not identical with it. In osteogenic sarcomas, types of bone develop which are in essential characteristics different from any other type of bone in the normal body.

The anaplasia of tumor cells has been explained by others as a consequence of atypical mitotic cell division which is often seen in cells of malignant tumors.

The daughter cells, after such an irregular mitotic division may have lost parts of chromosomes or whole chromosomes, and thus some of the genetic substance responsible for their differentiation and necessary for the maintenance of the level of differentiation This hypothesis does not seem reasonable because, in many tumors, the level of differentiation is the same for most of the cells although it is impossible to assume that all these cells have lost the same part of their chromosome set

Instead the loss of differentiation seems to be proportionate to the rate of growth of a tumor as the primary factor During mitotic division each cell reverts to a slightly lower level of differentiation as a consequence of the great changes in the nucleus as well as in the cytoplasm during this period The disappearance of the nuclear membrane and the isolation of the chromatin substance of the nucleus as chromosomes, the migration of the centrioles and differentiation of the spindle the changes of mitochondria and the Golgi apparatus, and finally the preparation for and the mechanism of division of the cytoplasm combine to force the dividing cell to give up to some measure, its specialization Normally the daughter cells regain their former level of differentiation soon after the nuclei reach the resting phase A certain tempo of cell division is necessary to maintain the normal differentiation of cells that is, the mitotic division itself, and especially the rest between two division periods, must be of a certain minimal duration.

If one assumes that the carcinogenetic stimulus, whatever it may be acts upon cells to speed the mitotic multiplication In other words, to shorten the interval between one cell division and the next these cells will permanently lose a certain degree of differentiation The pathologically shortened rest period after mitosis would not suffice to permit normal recovery of the specific differentiation of the dividing cell. The daughter cells would remain at a lower level of differentiation and the dedifferentiation would even be of greater degree in the following generations of cells, until a new equilibrium is reached between the rate of proliferation and the level of differentiation If this state is reached or if the rate of growth of a tumor decreases, differentiation of the cells is again possible The cells, having lost their former specialization to a greater or lesser degree can now develop their potentialities along lines divergent from their state of differentiation in the mother tissue

Progressive differentiation does not always coincide with loss of potentialities. It means merely that the differentiation makes their realization impossible. The term dedifferentiation is, therefore, an apt one, signifying the loss of differential qualities and of organoids and opening the way to differentiation according to the latent potentialities of a cell Dedifferentiated liver cells in a carcinoma may form liver cells and bile duct cells. Dedifferentiated bronchial epithelium may develop into mucus-producing cells. Dedifferentiated renal cells may develop into renal or adrenal epithelium Dedifferentiated connective tissue cells may differentiate into fibroblasts chondroblasts, or osteoblasts.

Atypical mitosis (Figs. 235 and 236) is, according to this interpretation, also a consequence of acceleration of the mitotic rhythm. Loss of differentiation and irregularity of cell division have a common cause An abnormally short

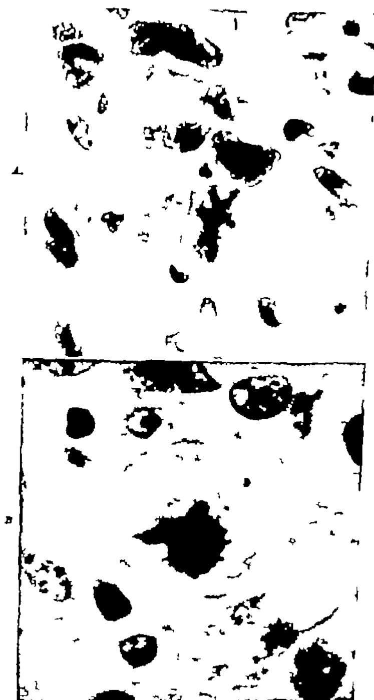


Fig. 235.—Atypical mitoses, pleomorphism, and hyperchromatism of malignant tumor cells. (Magnification ×1300.) (Specimens, courtesy New York Institute of Clinical and Oral Pathology, Inc.)

A, From an osteogenic sarcoma of the mandible of a forty-three-year-old woman.

B, From a osteogenic sarcoma of the mandible of a fifteen-year-old girl.

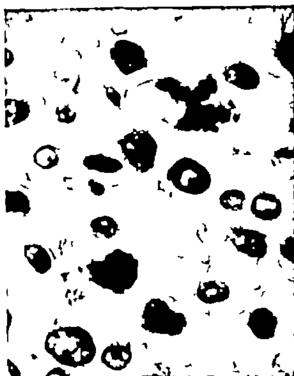


Fig. 236.—Atypical mitoses, pleomorphism, and hyperchromatism of the cells of a fibrosarcoma. (Original magnification ×1100 reduced ([illegible]) (Specimen, courtesy Army Medical Museum.)



Fig. 237.—Atypical mitoses, pleomorphism, hyperchromatism, and multinucleated giant cell in a fibrosarcoma. (Original magnification ×1100 reduced to [illegible]) (Specimen, courtesy Army Medical Museum.)

span between two consecutive cell divisions could lead to premature division of the centrioles and to the inclusion of three or more in one of the daughter cells. The presence of supernumerary centrioles could explain multipolar cell division

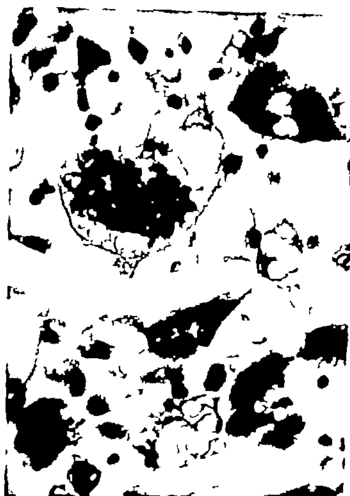


Fig. 238.—Tumor giant cells containing phagocytized red blood cells. Same case as shown in Fig. 236, B (Magnification ×1300.)

The frequent observation of uninuclear or multinuclear giant cells in highly malignant tumors (Figs. 237 and 238) could also be regarded as having the same primary cause the acceleration of cell proliferation. The division of the cytoplasm could be suppressed if the daughter nuclei, immediately after their separation, began to divide again. If the nuclei fuse, uninuclear giant cells will develop

The irregularities of precocious cell division are responsible also for the pleomorphism of the cells (Figs. 235 to 237) by unequal division of nucleus and cytoplasm Still another consequence of acceleration of proliferation in malignant tumors is the hyperchromatism of the nuclei. It is well known that the chromatin is more concentrated in the later stages of the prophase and in the

early stages of the telophase The dispersal of the chromatin indicates a rest period between cell divisions. Shortening or elimination of the rest period would account for the seemingly greater mass of chromatin substance in most cells of a malignant tumor

In the light of this hypothesis, the higher malignancy of a tumor as expressed by its rapid growth would be the cause of dedifferentiation or anaplasia, of its cells and not the consequence of their low level of differentiation This reversal of cause and effect would not of course diminish the prognostic value of the histologic findings of a lower or higher differentiation of tumor cells. A low level of differentiation will always signify a high degree of malignancy and vice versa

CLASSIFICATION OF PRIMARY TUMORS OF THE SKELETON

Classification of tumors of the skeleton is one of the difficult problems of pathology The difficulties stem in part from a lack of clear differentiation between bone as a tissue and bone as an organ To a greater degree the difficulties arise from the protean polymorphism of the tumors. Originating from more or less differentiated connective tissue the tumors show all the potentialities of young connective tissue. The benign tumors of connective tissue, in a stricter sense, can and sometimes do form cartilage and more frequently bone. The dedifferentiated connective tissue cells in malignant tumors of the skeleton have many more potencies. Therefore, a variability of the histologic picture even in different regions of the same tumor is quite common Transitions from one type to the other are innumerable. It is therefore, understandable that many authors do not consider so much the histologic picture but take as a means of subdivision the clinical behavior of these tumors This is especially true of those malignant growths of the skeleton which have been called osteogenic tumors because of their development from bone-forming tissue. Even the best classification of this group is based on the prominence of certain structural qualities in certain tumors which to a lesser degree are common to all osteogenic sarcomas.

To divide the tumors of the skeleton according to the mother tissue is possible only in so far as the tumors of the supporting tissues are separated from those of the accessory tissues of the skeleton Although the benign tumors of the supporting tissues of the skeleton can be subdivided into fibroma, chondroma and osteoma, one reservation must be made While an osteoma can be regarded as a tumor of bone tissue, a similar tumor may arise from secondary ossification of a fibroma. The same is true of a chondroma or an osteochondroma In the malignant group it is doubtful whether a fibrosarcoma in its pure form ever arises from tissues of the skeleton Although fibrosarcomas sometimes arise from the outer layer of the periosteum, more often they originate from extraskeletal connective tissue for example fasciae and tendons.

In using the terms osteogenic tissue and osteogenic sarcoma one should not forget that bone formation is not a faculty or function exclusively of the connec-

tive tissue which forms part of the skeleton. It is well known that, under suitable experimental conditions and in pathologic cases, cartilage or bone may be formed almost anywhere in the connective tissue.

In Table VI is given a classification of the primary and secondary or metastatic, tumors of the skeleton according to the mother tissue.

TABLE VI

TUMORS OF THE SKELETON

TISSUE OF ORIGIN	BENIGN	MALIGNANT
	Primary Tumors	
Supporting tissues		
Connective tissue	Fibroma (Ossifying)	Fibrosarcoma
	Myxoma	
Cartilage	Chondroma (Ossifying)	Osteogenic sarcoma
	Osteoma	
Bone—Osteoblasts	Osteochondroma	
Accessory tissues		
Blood vessels	Angioma	Angiosarcoma
Adipose tissue	Lipoma (?)	Liposarcoma
Bone marrow		
Blood forming elements		Multiple myeloma
Reticulum		Ewing's tumor
	Secondary Tumors	
Epithelial		Metastases of carcinoma
Mesodermal		Metastases of sarcoma

REACTION OF BONE TO THE GROWTH OF TUMORS

Bones react to the growth of tumors in very much the same way whether the tumors are benign or malignant, primary or secondary This reaction is also in dependent of whether a skeletal tumor is soft or is bone-producing With rare exceptions, which will be discussed later the reaction of bones can be regarded as a combination of two principal changes. The first is characterized by the resorption of bone tissue caused by growth of the tumor the second is character ized by the production of new bone, compensating for the loss of bone and developing mainly under functional stimuli.

The resorption of bone adjacent to a growing tumor is caused by pressure from the enlargement of the tumor Histologically it is not resorption by action of the tumor or the tumor cells. No tumor cells, as far as is known, can resorb bone. This is true not only of the epithelial cells of a carcinoma, but also of the mesodermal cells of a sarcoma. The normal connective tissue between tumor and bone is the matrix for the differentiation of osteoclasts (Fig. 239) which, as in other cases, differ greatly in size and in number of nuclei. An indication of the inability of a tumor to resorb bone *is the common* observation of cessation of resorption of bone when the tumor itself, in the absence of intervening normal connective tissue, comes in contact with bone. It is for this reason that spicules of bone are frequently found included in the tumor not unlike sequestra found in pus in osteomyelitis (Figs. 240 and 241)

The compensatory formation of new bone can take place in different ways, dependent very probably on the rate of concomitant bone destruction. If the tumor grows slowly and bone destruction therefore proceeds at a moderate rate new bone may be formed much in the same way as during normal growth The compact cortical layer of a bone for instance, may be resorbed from within and in compensation, a layer of lamellated mature bone is laid down on the periosteal surface and may even be replaced by Haversian systems In spongy bone the presence of a slow growing tumor may cause resorption on the surface of

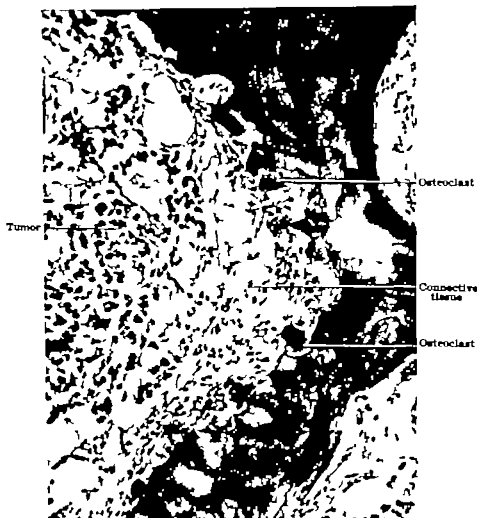


Fig. 239—Osteogenic sarcoma of a vertebra. Osteoclastic resorption of bone by the cells of connective tissue between tumor and bone (Original magnification ×250 reduced to ⅔)

trabeculae facing the tumor and compensatory formation of new bone may take place on the opposite surface of the trabeculae (Fig 242) thus leading to a pseudoshifting of an entire system of bony plates. The interplay between resorption and formation of new bone is often responsible for gradual changes in shape of the bone and descriptions such as curving bending expanding or swelling of a bone must be regarded in the light of the described changes.

If the destruction of bone by a tumor is rapid, compensatory formation of new bone, and thus compensatory strengthening of the weakened bone is also rapid. In most instances, the emergency repair is accomplished by the development of a peculiar type of spongy bone, the osteophyte. The term osteophyte should be used merely in a descriptive sense, because formation of bone in an



Fig. 240.—Osteogenic sarcoma of the maxilla. Remnant of the premorbid bone entirely surrounded by tumor cells. Resorption has ceased. (Original magnification ×250 reduced to ¾.) (Specimen, courtesy New York Institute of Clinical and Oral Pathology Inc.)

osteophytic arrangement is not confined to any specific skeletal disease. Osteophytes are formed quite often on the surface of compact bone as trabeculae arising roughly at right angles to the surface and joined at some distance from the old bone by trabeculae running parallel to the old surface (Figs. 243 and 244). The latter trabeculae sometimes form more or less continuous thin bony plates and may themselves give rise to a second outgrowth of osteophytes. In this way an emergency framework of bone is erected on the surface

of the old bone, to be replaced by compact bone at a later stage Because develop rapidly the osteophytes consist of immature, coarse-fibrillar (Fig 245)

Some authors believe that the compensatory formation of new bone defense reaction of the organism an attempt to wall off the growing tu This interpretation of the formation of new bone is no doubt incorrect shows almost no resistance to a growing tumor and is unable to check it pansion. Connective tissue is much more resistant to the pressure exerte a proliferating benign or malignant growth.

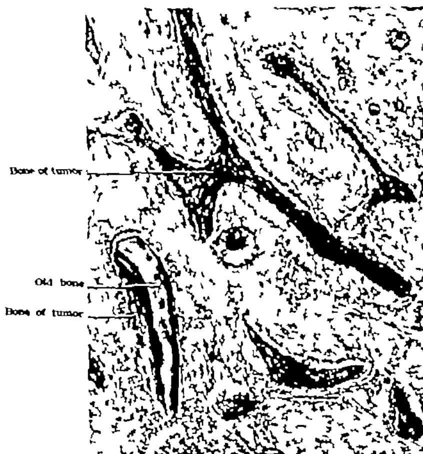


Fig. 241.—Osteogenic sarcoma of the femur Bone identical to that formed in the t itself is being pposed to a remnant of premorbid bone. (Original magnification ×12(duced to)

The changes in the periosteum during compensatory bone formation described in the literature as an elevation of the periosteum from the ori surface by the apposition of new bone. This description creates the im sion of a purely passive behavior In reality the periosteum grows with growing bone and we deal here with an active, coordinated biologic process.

At the shaft of a long bone, where the newly formed bone joins the morbid bone, the new bone seems to project from the old in a wedge-sh layer This lipping of the periosteum is clearly visible in roentgenog

Bone apposition

Bone resorption

Fig. 211.—A bone trabecula from an osteogenic sarcoma of the femur Resorption on one surface. Apposition of bone at the opposite surface. (Original magnification X200 reduced to)



Fig. 212.—Osteogenic sarcoma of a femur General vie . Osteophytes on the outer surf ce of the compact bone (Original magnification X3 reduced to $^{4}/_{5}$)

and constitutes an important factor in the diagnosis of certain tumors of bone. Its significance is much better understood if we look upon the formation of new bone as a mechanical compensatory reaction The similarity of the spur of bone in the development of tumors to the anchoring bony callus becomes apparent (see page 319) In other words the newly formed bone exceeds the



Fig. 244.—High magnification of an area shown in Fig. 243 Osteophytes in there on the outer surface of the compacta. (Original magnification ×49 reduced to ⅚)

tumor in extent proximally and distally and for this reason the spur is visible even after the tumor has caused resorption of the newly formed bone with which it is in contact.

Cartilage in the epiphyseal plate or articular cartilage, is known to be very resistant to the encroachment of a tumor A tumor is often separated from the cavity of a joint by articular cartilage and grows into the cavity only if this cartilage suffers mechanical injuries after it has lost the support of the under lying bone The explanation for this behavior of cartilage is found in the fact

that uncalcified cartilage is almost immune to resorption. Calcification of cartilage on the other hand, is dependent on preceding degenerative changes of its cells. Normal, vital and, therefore, noncalcifying cartilage persists despite progress of the tumor

In many cases, the destruction of bone proceeds at a greater rate than the compensatory formation of new bone, and pathologic fractures are the consequence. In rare cases, the compensatory formation of new bone may at least for a time, outstrip the destruction of bone the result is sclerosis of the involved part of the skeleton.

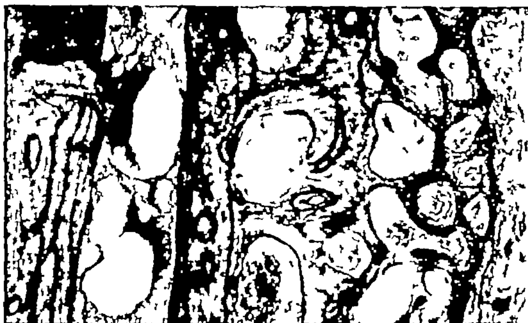


Fig. 245.—Detail of section shown in Fig. 244 The osteophytes consist of immature bone, parts of which have been replaced by mature bone. (Original magnification ×100; reduced to)

Metastases of certain epithelial tumors, especially carcinomas of the bladder and the prostate, seem to induce production of bone. If the cells proliferating from metastasis of a prostatic carcinoma invade the marrow spaces of a bone, formation of new bone can be observed on all or most of the bony surface adjacent to the tumor *This ability of the tumor cells to induce osteoblastic bone formation* from the connective tissue covering the bone is said to stem from a peculiar richness of the tumor cells in phosphatase. Experiments have shown that transplantation of the mucosa of the urinary bladder will in certain regions of the body induce the surrounding connective tissue to form bone.

BENIGN TUMORS OF THE SUPPORTING TISSUES OF THE SKELETON

The term supporting tissues is used here instead of connective tissues to avoid the complications which arise from the general and specific meaning of the latter term. The supporting tissues are characterized by an abundance

rcellular substance. In all these tissues, the intercellular substance it
isists of fibrils, sometimes arranged in fibers, and a cementing substance
; fibrils and cells together Of the different types of connective tissue,
connective tissue is most abundant in the skeleton It consists of a more
dense network of bundles of collagenous fibers and a variable number
lie fibers. There is little cementing substance The cells, fibroblasts, are
with long branching processes and dependent for their shape on the ar
ent and density of the fiber bundles in and between which they are found.
mber of cells varies in reverse ratio to the density of the fibrous elements.

mors arising from the connective tissue of the skeleton are not only
ons of the dense connective tissue, but also may simulate a type of tissue
is not found in the adult body This type, the mucoid connective tissue,
s found in man only in the umbilical cord where it is known as Wharton s
s characterized by an abundance of a gelatinous cementing substance
contains mucin The cells have fine processes which anastomose with
f neighboring cells. The collagenous fibrils are arranged in a network of
indles. The specific properties of the mucoid connective tissue are not
so much on the chemical nature of the cementing substance as on its
ince. Mucin or mucoids are present in the cementing substance of all
f connective tissue, cartilage and bone

rtilage of the skeleton is mostly hyaline Fibrous cartilage is found
in the intervertebral discs and the discs and menisci of articulations and
nally in the otherwise fibrous covering of the articular surfaces in the
omandibular joint To facilitate understanding of the development and
of the cartilage in tumors and to avoid misinterpretation of histologic
s, it must be pointed out that hyaline cartilage grows by interstitial as
by appositional growth. In this respect, it represents a transitory stage
connective tissue and bone. Wherever hyaline cartilage is covered by or
ontact with *connective tissue, layers of new cartilage are added by dif*
ation of young connective tissue cells into cartilage cells, chondro-

The histologic picture is that of an almost continuous and gradual
ion of the dense connective tissue of the perichondrium into cartilage
eeper layers of the perichondrium are much richer in cells than are
perficial layers. The densely arranged fiber bundles of the superficial
are split more and more into thinner strands of collagenous fibers rather
distributed between the cells. In the transition zone the small cells be-
rounded and produce hyaline intercellular substance which incorporates
rils of the connective tissue The most superficial layers of cartilage
aracterized by small closely packed cells. The deeper the layer of the
ge the larger are the chondrocytes and the farther from one another
e of the increase in hyaline substance produced by the cells. Here
lls are arranged in groups and are surrounded by areas of intercellular
nce of changing stainability the so-called cell territories. A regular
gement of the cells in columns is not found in hyaline cartilage except in
ne of proliferation in epiphyseal and articular cartilages.

Appositional growth of cartilage is usually combined with interstitial growth In some cartilages interstitial growth is predominant. In others growth is mainly by apposition in one dimension and interstitially in another dimension. Growth of articular cartilage occurs almost entirely by interstitial growth since this cartilage lacks a perichondrium. Only at the borders, where articular cartilage is continuous with the periosteum, is apposition of new cartilage by differentiation of this connective tissue possible. This zone showing a gradual change of connective tissue into cartilage has been mistaken for precartilaginous tissue Epiphyseal cartilage grows in thickness interstitially only in width, partly by apposition from the perichondrium. The secondary or accessory cartilage of the mandibular condyle, which is covered by fibrous tissue shows typical signs of appositional growth (page 108)

To understand all the different types of bone observed in the tumors of the skeleton and especially in the osteogenic sarcoma, one must keep in mind that, even in normal development and during regeneration (healing of fractures) two different types of bone tissue are formed One, the immature, or coarse-fibrillar is not only the type of bone which forms first in the development of the skeleton, but also the characteristic type of bone in periods of rapid growth of bone. In periods of slow formation of bone, the second type of bone tissue, lamellated bone is laid down. This type of bone seems functionally superior to immature bone, and therefore the coarse fibrillar bone is gradually replaced by lamellated bone, the only type of bone tissue found in the adult skeleton except in the otic capsule. The term trabecular bone is often used as synonymous with immature or coarse fibrillar bone This usage is incorrect although it is true that immature bone is always laid down as spongy or trabecular bone spongy bone of the adult consists of the same type of bone tissue as does compact bone namely mature or lamellated bone. Spongy and compact bone differ only in arrangement of the lamellae.

The fact that the bone in slow-growing osteoma is of the mature or lamellated type and that the bone in fast-growing especially malignant, tumors is of the immature or coarse fibrillar type is understandable in the light of our knowledge of the normal histogenesis of bone. Some types of bone occurring in tumors can only in a very general sense be termed immature. They are, in reality of a much more primitive structure than the immature bone of the normal fetus.

Fibroma

Fibroma of the skeleton is relatively rare except in the facial skeleton. Especially on the alveolar process of the jaws, fibromas are frequently found, sometimes in symmetrical arrangement. Some fibromas" of the oral cavity are in reality late stages in the healing of giant-cell nodes (see page 2ↄ8)

A fibroma consists of dense connective tissue. Rarely are the two elements, fibroblasts and collagenous fibers, found in the same numerical ratio and in the same topographic relation as in normal dense connective tissue. The lat

ter is characterized by the presence of compact bundles of collagenous fibers crossing one another in a functional arrangement. In the bundles themselves there are relatively few fibroblasts, and these are adapted in shape to the available spaces. Between the bundles is found a scant amount of loose connective tissue which is somewhat richer in cells and surrounds the small branches of blood vessels, lymph vessels, and nerves.

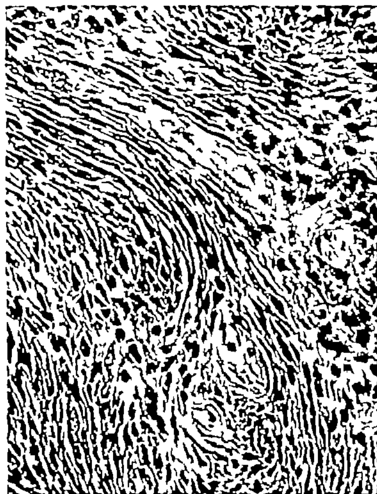


Fig. 246.—Fibroma showing fibers arranged in whorls. (Original magnification ×100 reduced to ⅔.) (Specimen, courtesy Army Medical Museum.)

Some polypous growths of the oral mucosa show a texture identical to that of normal connective tissue and it is questionable whether these fibromas can be classified as tumors. They probably represent the response of the mucous membrane to chronic irritation for example, pressure from dental protheses. In most fibromas the collagenous fibers are not arranged in bundles but show instead, a more or less even distribution of the fibers. The number of cells in a fibroma is usually greater than the number in normal connective tissue. The cells are more or less evenly distributed between the fibers and the fibers

are arranged in waves or whorls (Fig 246) *The consistency of a fibroma* depends on the ratio between cells and fibers. The color of a fibroma varies from pale pink to bright red depending on the number of blood vessels.

Fibromas enlarge slowly over many years, but, like all true tumors, have an unlimited capacity for growth The changes which may occur in a fibroma are twofold on the one hand, degeneration, usually of the mucoid type, and necrosis may occur in the central part of the tumor and degenerated tissue, may as elsewhere in the body undergo direct calcification. On the other hand. progressive differentiation may be observed in the connective tissue of the

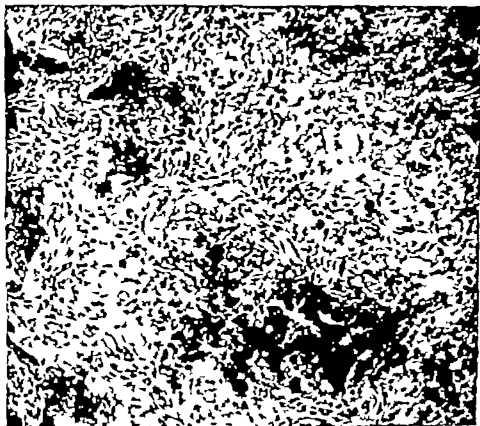


Fig. 247 —Ossifying fibroma of the maxilla. Early stage in the formation of bone. (Magnification ×120)

fibroma Formation of cartilage is rare formation of bone is fairly common Bone tissue develops in a fibroma in the same way as in normal membrane bones. Increase condensation, and hyalinization of the intercellular substance are first *observed (Fig 247) followed* by calcification of the osteoid substance (Fig 248) The result is immature, coarse, fibrillar bone arranged in a three-dimensional network of trabeculae (Figs. 249 and 250) Only rarely is the development of mature, lamellated bone observed (Fig 251)

In different fibromas, the fibrous tissue is of a different level of differentiation but even in one and the same tumor areas of connective tissue of different structure can be found for example, areas showing a greater or lesser number



g 248.—Immature bone of low level of differentiation in an ossifying fibroma. (Original mag nification X120 reduced to [illegible].) (Specimen, courtesy Army Medical Museum.)



Fig. 249.—Ossifying fibroma of the maxilla. Same specimen as shown in Fig. 247 Surface of the tumor. The immature bone trabeculae are partly covered by osteoid tissue. Bone apposition progressing in many areas. Reversal lines in some of the trabeculae. (Magnification ×120.)

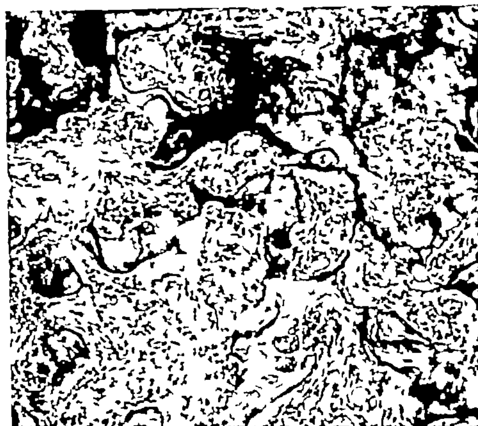


Fig. 248.—Ossifying fibroma of the maxilla. Same specimen as shown in Figs. 247 and 249. Resorption and apposition of bone in the center of the tumor. (Magnification ×120.)



Fig. 251.—Ossifying fibroma of the jaw with the symptoms of leontiasis ossea. Surface of tumor formed of mature spongy bone. Acti[ve] apposition in progress. (Original magnification ×120 reduced to ⅘.)



Fig. 242.—Ossifying fibroma of the jaw. Same specimen as shown in Fig. 241. Immature bone in the depth of the tumor. (Magnification ×120.)

of cells and fibers of varying diameter It is only natural that bone developing in these different tissues is of a different structure. It is for this reason that not only different ossifying fibromas may contain bone of different maturity but also in one tumor the bone may not be uniform (Figs. 249 and 250) Although immature bone as we find it in normal development is most in evidence, bone can be found which is less differentiated than bone seen even in the earliest stages of normal ontogenesis (Figs. 252 and 253) This bone is characterized by the thickness and irregularity of its fibrils, by the roundness of its cells,

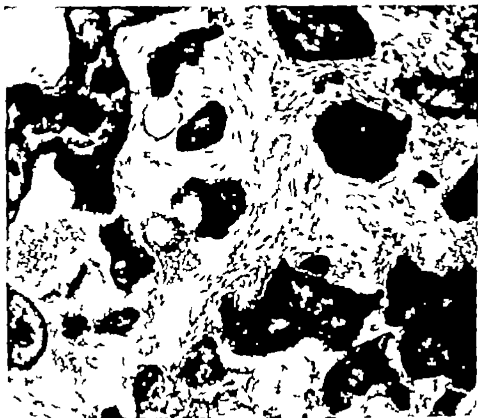


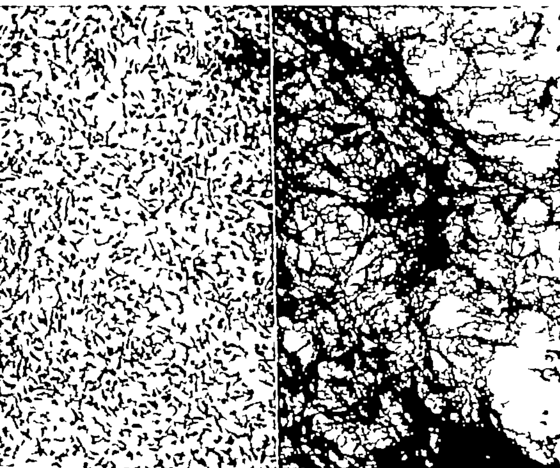
Fig. 253.—Ossifying fibroma of the maxilla. Same specimen as shown in Fig. 252. Foci of calcification (Magnification ×120)

which have only a few processes and are irregularly arranged, and finally by its strong basophilia It has been called blue bone Calcification is often retarded.

If the ossification of a fibroma is advanced, differentiation between an ossifying fibroma and an osteoma may in some cases, be difficult. Generally these two types of tumor are characterized by the following divergent qualities Bone of fibroma is always spongy bone and only rarely shows a cortical layer which simulates compact bone The bone is, for the most part, immature. An osteoma sometimes consists of compact bone only or shows at least a cortical layer of compact *lamellated bone* *Even if spongy bone* constitutes the central portions, it is usually mature and lamellated.

Myxoma

A tumor consisting of mucous connective tissue, termed a myxoma, is generally likened to similar types of embryonic tissue, especially Wharton's jelly of the umbilical cord and the embryonic mesenchyme. Primary myxomas are said to arise from islands of persistent embryonic tissue. Secondary myxomas develop by mucoid degeneration of other tumors of supporting tissues, for example, fibroma and chondroma. A spurious type of myxoma arises from edematous changes in a fibroma (Figs. 254 B, 255 B).

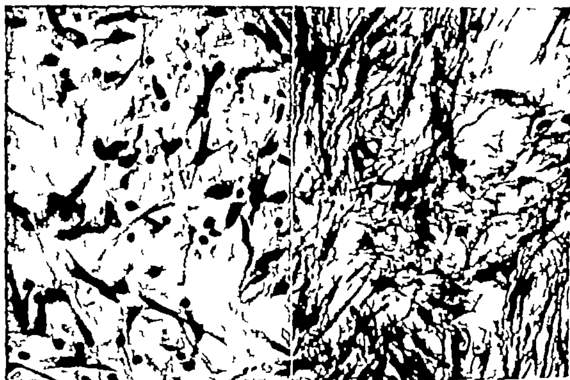


A. B.

Fig 254.—A, Myxoma of the jaw. (Original magnification ×150, reduced to ⅘.) B, Pseudomyxoma of the jaw. (Original magnification ×150, reduced to ⅘.) (Specimens, courtesy New York Institut of Clinical and Oral Pathology, Inc.)

A myxoma is characterized by an abundance of gelatinous homogeneous intercellular substance which contains mucus or mucuslike substances, mucoids. It has the typical reaction of mucus, being strongly basophilic. The cells of the tumor are irregularly star shaped, or stellate, anastomosing with one another by their long processes. Fibrils or fibers are few or are absent. Sometimes formation of bone occurs in a myxoma (Fig. 256).

It has been pointed out that the similarity of the tissue of a tumor to that of the fetal or the mature body is often only superficial and never to be taken as proof of a genetic relation. Furthermore, it has been shown that the tissue of tumors is often of an aberrant type, never encountered in normal development. This variability in tumor tissue, which goes far beyond that of the normal tissues of similar type, is, it seems, one of the most important aspects of tumor development. It is proof of the irregularity and independence of the tumor as is its quantitative growth potential.



A. B

Fig. 255.—High magnification of areas shown in Fig. 254.
A Myxoma. (Original magnification ×[illegible] reduced to [illegible].)
B Pseudomyxoma. (Original magnification ×[illegible] reduced to [illegible].)

The myxoma from this point of view is proliferative connective tissue, with a specific ratio of cells and intercellular elements, which resembles embryonic mucoid tissue and which may arise any place in the mature body where loose connective tissue is stimulated to neoplastic proliferation Loose connective tissue consists of three principal elements the cells (fibroblasts) the collagenous fibers, and the amorphous cementing substance which binds cells and fibers. This substance which is semifluid or gelatinous, contains proteins and mucoids Overproduction of an amorphous intercellular substance, accompanied by failure of differentiation of collagenous fibers, causes an increasing similarit to embryonic mucoid tissue.

A secondary myxoma develops by mucoid degeneration of a fibroma or chondroma. These cases seem to involve a change in the colloid phases during which the mucoid-containing cementing substance expands and the fibers and fibrils apparently disappear. The end product of this degeneration may be so similar to the histologic picture of a primary myxoma that a differential diagnosis is impossible without a detailed history of the case.



Fig 256—Formation of bone in a myxoma. Same specimen as shown in Fig 254. (Original magnification ×150 reduced to $\frac{4}{5}$.)

Primary myxoma of the skeleton, which is rare, may develop from the periosteal as well as from the endosteal connective tissue. It grows slowly and, if it arises in the marrow space, its development will gradually cause resorption of the surrounding bone with compensatory production of new bone in the periphery.

Since mucoid degeneration involves often only parts or lobes of a fibroma or chondroma, secondary degenerative myxoma is often combined with remnants of the original tumor. The result is a fibromyxoma or chondromyxoma.

Chondroma

Tumors which consist, at least primarily, of cartilage are termed chondromas. This cartilage is, in most cases, hyaline, but a chondroma may consist

partly or entirely of fibrous or even elastic cartilage. The true chondroma must be distinguished from hypertrophy of cartilage. The latter may either protrude from the outer surface of a bone as an ecchondrosis, or it is, more rarely found inside the marrow cavity of a bone as enchondroma. These cartilaginous growths lack one important characteristic of a tumor the unlimited growth potential, following as they do, the general growth curve of the individual and ceasing to grow after puberty

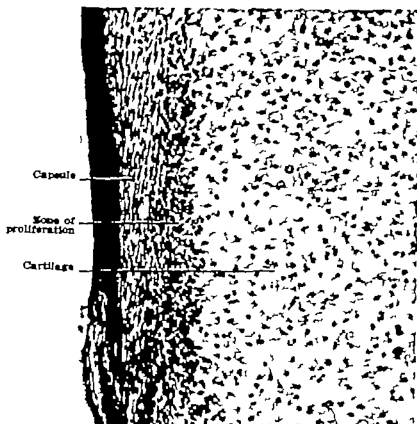


Fig. 257 —Encapsulated lobe of irregular hyaline cartilage from an osteochondroma of the mandible. (Original magnification ×130 reduced to ⅘)

The ecchondrosis seems always to originate from existing cartilage. The epiphyseal plates, the articular cartilages, the cartilaginous part of the ribs, and the cartilage on the symphysis pubis are the most frequent sites. The assumption that we deal here with a hypertrophic overgrowth and not with a tumor is supported by the mode of origin of the ecchondrosis, in which abnormal differentiation of a tissue a characteristic of tumor development, is not observed.

As normal cartilage, the cartilage of an ecchondrosis may calcify, or it may be replaced by bone. Ossification follows the same sequence as in normal endochondral ossification. An ecchondrosis which is partially ossified is often referred to as an osteochondroma (Fig 259)

The most frequent sites of a true chondroma are the marrow cavities of the bones of the fingers and toes the sternum, and the ribs. Sometimes chondromas

re found in the vertebrae and in the metaphyseal region of the long bones, espe-ially of the lower extremities more rarely in other bones, for instance, in the andible (Fig 257)

A chondroma very often consists of several lobes of cartilage, separated rom one another by septa of connective tissue, which are continuous with the apsule of the tumor The growth of the tumor occurs generally by apposition or example, by differentiation of the deepest layer of the perichondral capsule nd septa into cartilage. This mode of growth not only is characteristic for the hondroma but also plays an important role in the growth of normal cartilage.

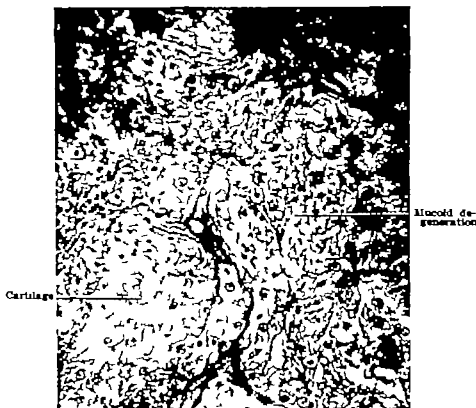


Fig. 256.—Areas of mucoid degeneration in a chondroma of the finger (Original magnification ×130 reduced to ⅔)

The chondroma has been thought by some authors to originate in remnants of the epiphyseal cartilage persisting in the spongy trabeculae of the shaft after the growth of a bone is complete. It is true that spicules of cartilage surrounded by bone may be found for some time deep in the shaft, even under normal conditions. However these pieces of cartilage consist of calcified intercellular substance only do not contain any cells, and are therefore not capable of growth. That under pathologic conditions, a piece of living cartilage could be isolated during growth changes in the metaphysis is open to question but is highly improbable.

The frequent observation of a multilobulated chondroma shows that development of new islands of cartilage from connective tissue is quite common. The

isolated nodules of cartilage superimposed on the primary node cannot develop by proliferation of the cartilage cells of the primary node. If this is true for secondary lobes of chondromas, it is, in all probability true for the primary growth. Why such chondromas develop frequently in the bones of the hand and foot cannot be explained. To assume that chondromas are derived from supernumerary joint cartilages is absurd just as is the supposition that they are derived from persisting embryonic (precartilaginous) tissue.

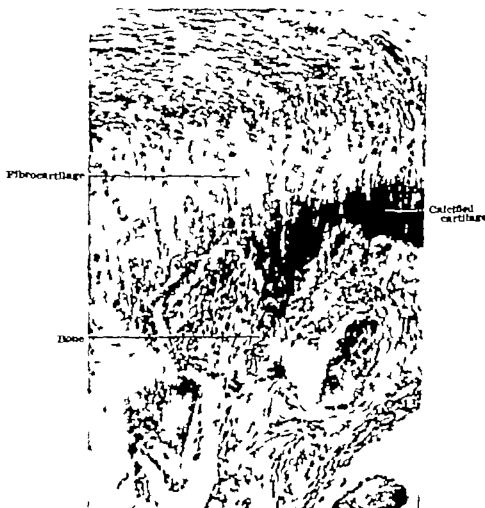


Fig 259 —Osteochondroma of the maxilla Resorption of calcified cartilage and formation of immature bone (Original magnification ×150 reduced to [illegible]) (Specimen, New York Institute of Clinical and Oral Pathology Inc.)

The cartilaginous tissue of a chondroma does not present the picture of normal hyaline cartilage in which the cells are more or less regularly arranged. Instead, the cells are irregularly distributed and of various sizes and shapes, and regions showing few cells alternate with regions in which the cells are numerous but small To term this latter type embryonic cartilage is incorrect since the similarity to normal embryonic tissue is only superficial. The hyaline intercellular substance of a chondroma may apparently be homogeneous. In other

regions, the fibers may remain more or less visible so that transitional stages between hyaline and fibrous cartilage frequently can be found. As has been mentioned, elastic fibers have been observed in a chondroma.

Chondromas may show changes in divergent directions. Degenerative changes lead either to calcification or mucous degeneration (Fig 258) sometimes with the formation of cysts. A progressive change is the ossification of a chondroma a process which occurs according to the laws of endochondral bone formation. Parts of the cartilage persist as a rule. A partly ossified chondroma is termed an osteochondroma (Fig 259)

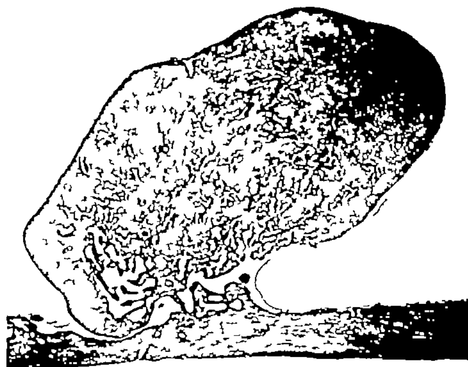


Fig 260—Exostosis or osteoma of the frontal sinus.

Osteoma

The differentiation of a true osteoma from other overgrowths of bone is difficult and has caused considerable confusion in the literature. To arrive at a fairly sound definition of osteoma not only limited hyperplastic growth of bone, but also secondary formation of bone in tumors of connective tissue or cartilage must be excluded. In spite of such a delimitation the clinical and sometimes even the histologic differential diagnosis will be impossible. An ossifying fibroma, for instance, may clinically and roentgenographically present the same picture as an osteoma. Under the microscope, an ossifying fibroma is, as a rule characterized by the presence of an immature type of bone, in many cases even by the presence of different types of bone in neighboring areas

(see page 400) Ossifying chondromas, on the other hand, may be in all details indistinguishable from a true osteoma because formation of bone to replace the cartilage of the primary tumor is generally slow and mature, lamellated bone is then found. Even a layer of cartilage covering the bony part of the tumor and the well known zone of endochondral ossification at the border between bone and



Fig 281 —Exostosis at the alveolar border in the region of the upper second molar

cartilage, cannot be regarded as the basis for a diagnosis of ossifying chondroma. It seems that, in some cases, the connective tissue covering a true osteoma may differentiate into hyaline cartilage, thus providing a growth zone for the osteoma This will occur when the surface of the tumor is under some pressure for instance, if the tumor is traversed by a tendon.

The hyperplastic overgrowth of bone is characterized by its limited growth potential. Its growth is usually retarded and finally ceases altogether without reaching any great dimensions. In most cases, hyperplasia of bone occurs on the surface of bones as an exostosis. More rarely it occurs in the marrow spaces as an enostosis. It is a matter of choice whether a bony growth protruding into one of the pneumatic cavities of the skull (Fig 260) is classified as exostosis or enostosis. An exostosis may consist (1) of compact bone with only a few or no haversian systems or (2) of more or less dense cancellous bone. The former is termed a compact or eburnated exostosis the latter a spongy exostosis. It may form flat or somewhat prominent elevations of bone or may be connected with the bone by a stalk (Fig 260) which may break or be resorbed the attached exostosis becoming free.

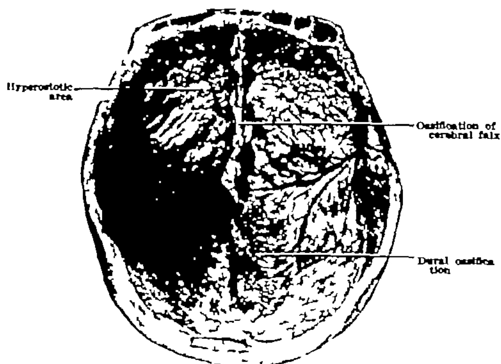


Fig 262.—Senile hyperostosis of the skull and extensive ossification of the falx cerebri. Woman sixty-seven years old (Specimen, courtesy Dr Th. Joh.)

Exostoses are frequently found on the bones of the skull. Flat prominences of compact bone are seen on the outer surface of the cranial vault. On the jaw bone they are frequently found in a definite location. One frequent site is the hard palate at the midline. The overgrowth of the palatine processes of the maxillary bones leads here to the development of the palatine torus, which is of varying size and shape and, in extreme cases, may form a mushroomlike growth, nodulated on its surface The next frequent site is the inner (lingual) surface

of the mandible in the anterior region, where the mandibular torus is formed, consisting of one or more irregularly rounded exostoses, situated approximately at the border between the body and alveolar process in the region of the incisors, canines, and premolars, and rarely in the molar region. Prominent mandibular exostoses may narrow considerably the anterior part of the oral

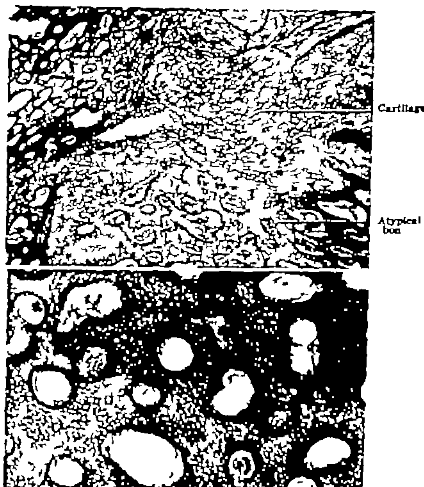


Fig. 262.—Osteochondroma of the mandible.

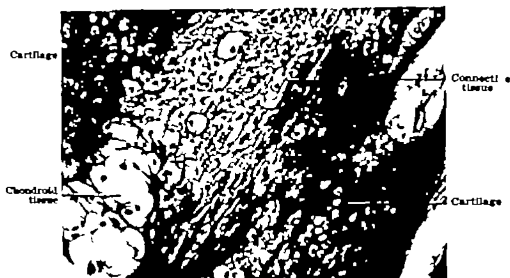
A Atypical immature bone, cartilage, and connective tissue closely associated with each other (Original magnification ×30 reduced to ⅘.)

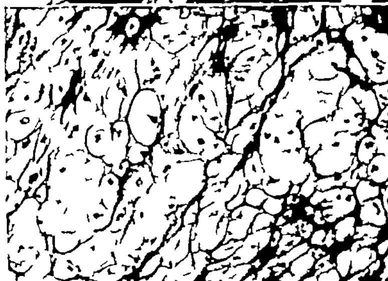
B Higher magnification of the immature bone. (Original magnification ×150 reduced to ⅘.)

cavity impeding the movements of the tongue. Small exostoses often develop at the free border of the alveolar process of the maxilla (Fig 261) but rarely at that of the mandible. They are confined to the external alveolar plate and are said to occur much more frequently in members of the Mongolian race than in other races. These alveolar exostoses never attain any appreciable size.

A favorite site of exostoses in the bones of the extracranial skeleton is the attachments of tendons. The development of exostoses of this type may be caused by an increased pull of the tendon upon the bone. Thus, the exostosis can be seen as the product of an exaggerated formative influence of muscle pull

A





B

Fig. 264.—Osteochondroma of the mandible. Same specimen as shown in Fig. 262. (Magnification ×260.)
A. Irregular hyaline and fibrous cartilage.
B. Cartilage of chondroid type.

leading to the development of crests, ridges, processes, etc. Sometimes, a tendon exerts pressure upon part of the exostosis, and it is in such cases that secondary cartilage develops on the surface of the exostosis. This cartilage may even function as a growth center for the exostosis, being gradually replaced by bone as in endochondral bone growth.

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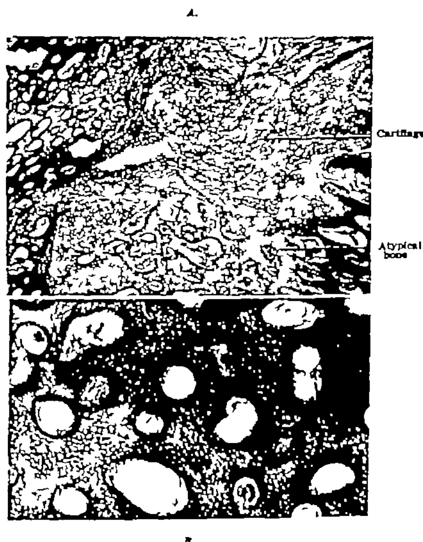


Fig 263 —Osteochondroma of the mandible.

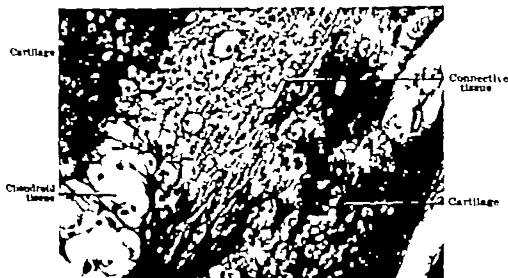
A Atypical immature bone, cartilage, and connective tissue closely associated with each other (Original magnification ×30 reduced to ⅔)

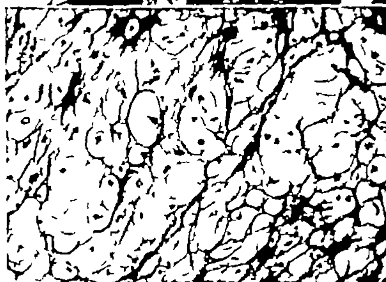
B Higher magnification of the immature bone. (Original magnification ×150; reduced to ⅔)

cavity impeding the movements of the tongue. Small exostoses often develop at the free border of the alveolar process of the maxilla (Fig 261) but rarely at that of the mandible. They are confined to the external alveolar plate and are said to occur much more frequently in members of the Mongolian race than in other races. These alveolar exostoses never attain any appreciable size.

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A





B

Fig. 244 —Osteochondroma of the mandible Same specimen as shown in Fig. 242. (Magnification X260)
A. Irregular hyaline and fibrous cartilage.
B Cartilage of chondroid type

leading to the development of crests, ridges, processes, etc. Sometimes, a tendon exerts pressure upon part of the exostosis, and it is in such cases that secondary cartilage develops on the surface of the exostosis. This cartilage may even function as a growth center for the exostosis, being gradually replaced by bone as in endochondral bone growth.

A typical overgrowth of bone is the senile hyperostosis of the skull or internal frontal hyperostosis (Fig. 262) It is generally restricted to the frontal area of the skull but not to a single bone. Frequently it is combined with ectopic bone formation in the dura mater The bones in the hyperostotic areas may thicken to three to four times their normal dimension but the increase in thickness is never even. The outer surface of the involved bones does not show any significant macroscopic changes, while the inner surface is irregular beset by flat, rounded smooth prominences of varying size. Arterial sulci in the involved region are greatly deepened, sometimes even closed to canals for a variable length by the apposition of bone on the cerebral surface.

Histologically the senile hyperostosis is characterized by apposition of lamellated bone on the inner surface of the bones, thus primarily increasing the thickness of the inner compact plate. A reconstruction of the involved bones soon leads to resorption of the inner compacta from the diploic marrow spaces and a replacement of a part of the compact bone by spongy bone. Thus the inner compact plate is kept at a moderate thickness, while the diploë increases its volume considerably

Despite the hypertrophy of the inner plate and the reconstruction of the diploë, there is little change on the outer surface of the involved bones. Only occasionally histologic examination reveals resorption on this surface. The seeming imbalance between the changes on the cerebral and pericranial surfaces may be due to the fact that the outer plate is part of the cranial superstructure and therefore largely under the influence of muscular and masticatory forces.

Internal frontal hyperostosis mostly affects women. The atrophic changes of the frontal lobes of the brain that can be caused by a variety of diseases seem to be the local cause for the bony overgrowth a hyperplasia e vacuo. The cerebral and cranial changes are often accompanied by obesity asthenia, and hirsutism. The combination of these symptoms is known as Stewart Morel's or Morgagni's syndrome.

True osteomas seem to be relatively rare. They are found in the skull, originating in one of the nasal sinuses or one of the bones of the orbit. They may reach enormous proportions. Other osteomas were observed growing from the inner surface of the mandible and reducing the oral cavity Osteomas may develop in the spongy substance or the marrow cavity of long bones. They are, generally slow-growing tumors, and for this reason it is difficult to make a differential diagnosis between an osteoma and an exostosis. The difficulty of a differential diagnosis is of minor importance since an exostosis or an osteoma will be removed only if it is of great size or if its position renders it a menace to the health or life of the patient.

Some benign tumors of the skeleton consist primarily of a mixture of tissues which are, as a rule, atypical. An osteochondroma of this type (Figs. 263 and 264) consists of a peculiar type of immature bone, of chondroid tissue, of atypical cartilage, and of dense connective tissue.

MALIGNANT TUMORS OF THE SUPPORTING TISSUES OF THE SKELETON

Because of their confusing variety the malignant tumors arising from the supporting tissues of the skeleton seem to defy classification Clinically and histologically there are three types of skeletal sarcomas, namely the fibrosarcoma, the chondrosarcoma and the osteogenic sarcoma

Fibrosarcoma

The periosteal fibrosarcoma (Fig 265) originates from the dense connective tissue of the outer layer of the periosteum and is a relatively well differentiated tumor rich in fibrous elements. It is whitish firm and usually well defined. It grows slowly and only rarely causes destruction of the neighboring bone Clinically it is characterized by a low grade malignancy

The existence of a central fibrosarcoma developing in the marrow spaces of long bones is doubted by some observers, who regard such tumors as osteogenic sarcomas that did not or had not yet produced bone However evidence has accumulated pointing to the occurrence of true central fibrosarcomas.

The central tumors are variable in their clinical and histologic behavior ranging from low to relatively high malignancy During their growth they cause erosion of the cortex and compensatory formation of new bone on the periosteal surface

Chondrosarcoma

Though formation of cartilage is seen not infrequently in osteogenic sarcomas, some authors recognize the chondrosarcoma as a separate disease entity It seems to develop as a malignant phase from benign cartilaginous overgrowths the cartilage of any one of the tumors in hereditary multiple exostoses may give rise to a peripheral chondrosarcoma while a central chondrosarcoma may develop from an enchondroma The chondrosarcoma is of a lower malignancy than the osteogenic sarcoma growing slowly and causing late metastases.

Histologically the chondrosarcoma is characterized by the irregularity of its cells. Multinucleated cells and also large cells containing one large nucleus are common. The fact that mitoses are reatively rare has led some authors to believe in amitotic proliferation of the chondrocytes.

Secondary changes in the chondrosarcoma are often of a degenerative nature for instance mucoid degeneration or calcification However formation of bone and progressive replacement of cartilage by bone have also been observed. It is not certain whether the latter change occurs during the malignant phase of the tumor

Osteogenic Sarcoma

The most frequent sarcomas originating from the supporting tissues of the skeleton, are the osteogenic sarcomas. This term was coined to signify the development of these tumors from potentially bone forming tissues. The loose

connective tissue from which these tumors develop does not only produce bone but often also cartilage. The term osteogenic sarcoma should therefore not be interpreted as presupposing the existence of a specific osteogenic tissue.

Though the osteogenic sarcoma is a tumor of adolescence and post adolescence that is, from 10 to 25 years it is by no means rare in older individuals. The tumors originate mainly in the near metaphyseal areas of the shaft. Most frequently involved are the femur tibia and humerus. Paget's disease is often complicated by the development of an osteogenic sarcoma, though the factors involved are not known.

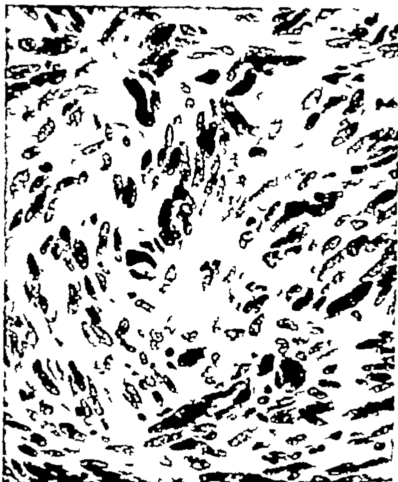


Fig. 265.—Fibrosarcoma. Pleomorphism and hyperchromatism of the cells. Relatively good development of fibers. (Magnification ×400.) (Specimen, courtesy Army Medical Museum.)

To understand the biologic meaning of the term osteogenic or chondrogenic tissue, the peculiarities of growth of cartilage and bone must be kept in mind. It has been pointed out repeatedly that cartilage not only grows interstitially but also that, in certain areas, appositional growth of cartilage takes place. Such appositional growth of cartilage is found at the margins of articular cartilage, which are covered by an extension of the synovial membrane at its insertion to the bone and thus possess a perichondrium. Appositional growth in this area

widens the articular cartilage. Epiphyseal cartilaginous plates grow in transverse diameter by apposition at their perichondral surface That bone grows by apposition only is, of course well known.

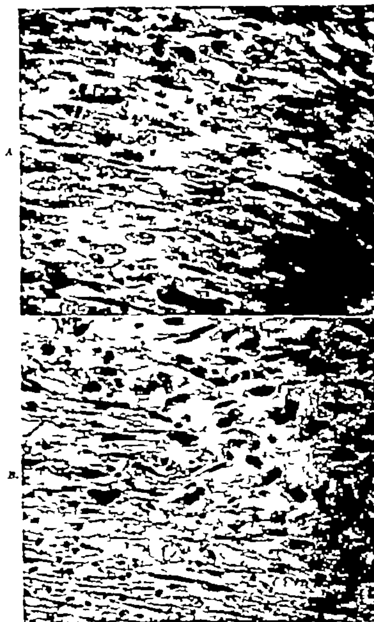


Fig. 244.—Osteogenic sarcoma of the tibia. (Original magnification ×400 reduced to ⅘.)
A Cellular area of the connective tissue.
B Fibrous area of the connective tissue of the tumor

One of the fundamental differences between interstitial and appositional growth is seen in the fact that in appositional growth a differentiation of cells of the growing tissue occurs throughout the period of growth, whereas in interstitial growth the specific and differentiated tissue cells produce cells on their

own level of differentiation. The growth of cartilage interstitially means that chondrocytes divide to produce chondrocytes. Growth of cartilage by apposition means that cells of the surrounding connective tissue, the perichondrium, *differentiate* into chondrocytes, and that this process has to repeat itself as long as the cartilage grows. Growth of bone by apposition means that cells of the surrounding tissue, periosteum or endosteum *differentiate* into osteoblasts



Fig. 207.—Osteogenic sarcoma of the head of the humerus. Not the striking differences in the structure of the tumor in adjacent areas. (Original magnification ×10 reduced to [illegible].)

and that this process also must be continued as long as the bone grows in order to replace the osteoblasts which are incorporated in the bone as osteocytes. New osteoblasts have to differentiate also after the disappearance of osteoblasts in periods of rest or after a period of resorption.

This peculiar type of growth is based on the presence of pluripotential cells in the connective tissue surrounding growing bone and cartilage. Although it is not correct to speak of these cells as undifferentiated, they are far less

differentiated than are the fibroblasts of dense or regular connective tissue. Whether they are identical with Maximow's undifferentiated mesenchymal cells is not certain. To identify these pluripotential cells of low differentiation with embryonic mesenchymal cells or to term the connective tissue in which they are found an embryonic tissue would also be erroneous. Although relatively un differentiated ' these cells and the connective tissue are highly differentiated as compared with embryonic mesenchyme



Fig. 344.—Osteogenic sarcoma of the femur Not the striking differences in the structure of the tumor | adjacent areas (Original magnification X10 reduced to ¾)

It would also be a mistake to ascribe a specific chondrogenic and osteogenic property to periosteum and endosteum since young connective tissue in any part of the body may have the same properties. Whether this potency of skeletogenesis is realized does not depend on the quality of the cell alone. A number of factors must combine to initiate production of bone for example, localized concentration of phosphatase and other unknown stimuli of chemical or mechanical nature

An excellent example of manifestation of skeletogenic properties is the formation of callus after fractures of bones. The young connective tissue organizing the primary blood clot arises only in part from periosteum or endosteum. Most of this young connective tissue or granulation tissue is derived from the interstitial loose connective tissue in muscles and around blood vessels and nerves. The cells of this young connective tissue are on a lower level of differentiation and therefore more versatile than are those of normal loose



Fig. 369.—Osteogenic sarcoma of a vertebra. Note the striking differences in the structure of the tumor in adjacent areas. (Original magnification ×10, reduced to ⅚.)

connective tissue. In this respect the cells of granulation tissue resemble the pluripotential skeletogenic cells, but again it would be erroneous to identify granulation tissue with embryonic mesenchyme.

The fact remains that the bones are surrounded by and contain pluripotential mesodermal cells which can be regarded as reserve material, elements of which differentiate into chondroblasts, osteoblasts, and fibroblasts. The presence of these cells is not restricted to any given part of the skeleton or to any given

time of life since the continuous reconstruction of bone necessitates apposition of new bone tissue after resorption of overaged bone or mechanically inadequate bone

The absence of such relatively undifferentiated cells in dense connective tissue or regular connective tissue seems to explain the infrequent formation of cartilage or bone in the fibrosarcoma of periosteal or extraperiosteal origin.



Fig. 270.—Osteogenic sarcoma of a vertebra. Not the striking differences in the struct re of the tumor in adjacent areas. (Original magnification ×10 reduced to)

To appreciate the biologic significance of the pluripotential cells of the skeleton or of young proliferating connective tissue, three different expressions of their normal their regenerative and their destructive activities should be compared that is, normal growth of a bone, callus formation following fracture, and the development and differentiation of an osteogenic sarcoma.

The skeletogenic cells on the outer surface of a developing bone differentiate for many generations into chondroblasts. Later generations of these cells in certain areas differentiate into osteoblasts, whereas the cells at the margins of

the articular cartilage and those in contact with the epiphyseal plate continue to take part in the appositional growth of cartilage Such a change in the direction of differentiation of those pluripotential cells occurs not only at the time of the first appearance of bone, but also later in life at the border line between the metaphysis and the epiphyseal plate and along the margins of the articular cartilage Growth of epiphyseal cartilage in longitudinal and transverse diameters and its replacement by the growing bone complicate the cellular process at a point where interstitial and appositional growth of cartilage and

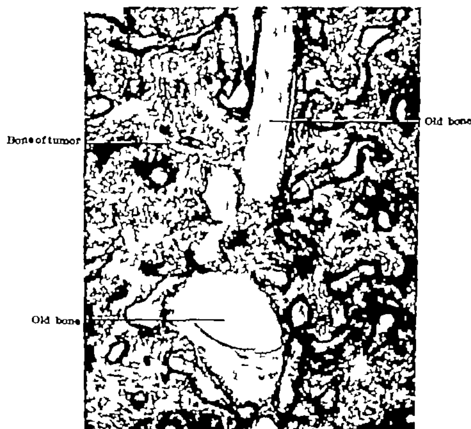


Fig 271 —Osteogenic sarcoma of the femur Note the difference between the premorbid lamellated bone and the highly immature bone of the tumor The latter shows the sclerotic type of tumor (Original magnification ×150 reduced to ⅝)

its resorption and replacement by bone occur in a restricted area at one and the same time. We can therefore draw two conclusions (1) Different generations of skeletogenic cells differentiate either into cartilage or bone cells (2) the region of greatest instability is the border between the metaphysis and the epiphyseal plate.

The versatility of the relatively undifferentiated, skeletogenic or potentially skeletogenic cells of young connective tissue easily can be evaluated in the formation of the callus. The cells of the granulation tissues, whatever their origin, may produce fibrous connective tissue, cartilage, or bone. The extent of each one of the three components of the callus is dependent on local conditions,

the extent of injury to the soft tissue, the position of the bone fragments, and mechanical stimuli. As in normal development of bone, the first bone formed in the callus is coarse fibrillar or immature bone which only later is replaced by lamellated or mature bone.

The term young connective tissue needs some elaboration. It expresses more than the fact that this tissue is richer in cells, poorer in fibers, and more richly vascularized than its mother tissue The term does imply that the cells,



Fig. 272.—Calcification of hyalinized connective tissue. Same specimen as shown in Fig. 271. (Original magnification ×150 reduced to ⅘)

having regressed to a lower level of differentiation, have regained the faculty of expressing their pluripotentiality The reason for their regression in differentiation and for the liberation of their potentialities seems to be the accelerated rate of their proliferation. It has been pointed out that each cell must lose some of its differentiation during cell division. During normal growth of the tissue, this loss, however is slight and temporary Acceleration of tissue formation and therefore, of cell division as it occurs in most regenerative processes will lead to a more marked and more prolonged lowering of differentiation of the dividing cells because the cells are not given enough time to recover their normal level of differentiation between two consecutive cell divisions. The acceleration of cell division is, in regenerative growth, still well within the limits of the normal biologic pattern. The result is the formation of a young but normal tissue.

In a malignant tumor, the growth and thus the multiplication of cells, is pathologically exaggerated. In a tumor therefore, the cells of the original tissue are not only dedifferentiated to a very low level but also their structure and their potencies are greatly distorted. These cells, if they reach a state of relative equilibrium, may again attain a higher level of differentiation and, if the tumor is of mesodermal origin, the cells may again begin the production of intercellular substances. The resulting tissue can be identified only rarely with a normal tissue. In most cases, the tissue of the tumor shows only some similarities to a certain normal type



Fig 273—Hyalinized connective tissue with a sprinkling of calcium salts. Same specimen as shown Fig. 271 (Original magnification X150 reduced to ¾)

As applied to the osteogenic sarcoma, this point of view makes it understandable why no other sarcoma shows such wide variation in its histologic structure It is extremely difficult not only to find two osteogenic sarcomas which have the same structure, but it is also impossible to find an osteogenic sarcoma consisting of one type of tissue in its entirety In fact, different areas of one and the same tumor may show surprising differences in structure. All this can easily be understood if we recall that the osteogenic sarcoma originates from pluripotential cells of relatively low differentiation. It is clear that the pathologic depression of the level of differentiation and the disorganizing effect of precipitous division will cause these cells to assume widely different shapes and widely dif- rent developmental potencies. Therefore not only does the

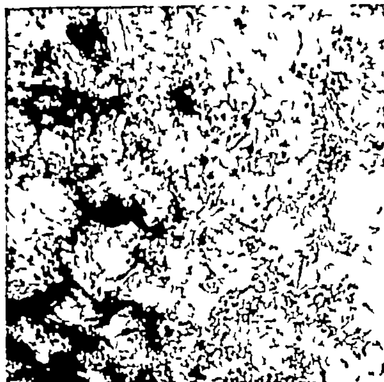


Fig. 374.—Osteogenic sarcoma of the head of the humerus. Network of trabeculae of highly immature partly uncalcified bone. (Original magnification ×120 reduced to [illegible])

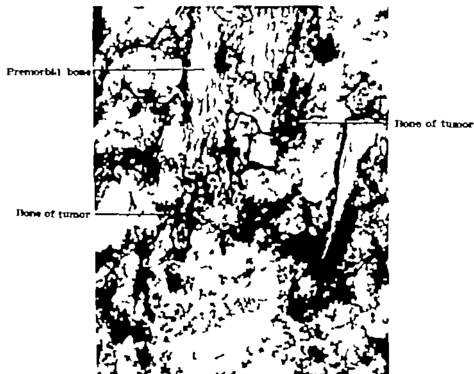


Fig. 375.—Irregular network of thin trabeculae of atypical and highly immature bone partly apposed on two remnants of premorbid bone. Same specimen as shown in Fig. 374. (Original magnification ×120 reduced to [illegible])

osteogenic sarcoma consist of connective tissue, cartilage, and bone, but also each one of these tissues shows innumerable variations. These different tissues are sometimes more or less similar to tissues found in some stage of normal human development. More often, they are entirely new and aberrant tissues, which could be called a new invention of the tumor cells.



Fig. 276.—Osteogenic sarcoma of a vertebra. A delicate network of atypical bone has been formed in the marrow spaces adjacent to an intact trabecula. (Original magnification ×160 reduced to ⅘.)

Connective tissue in an osteogenic sarcoma may simulate embryonic mesenchyme. Then a mucoid connective tissue is found with rather uniform star shaped cells with long processes. The intercellular substance is gelatinous and contains only a few slender fibers. Such an area of an osteosarcoma could be called a myxosarcoma. It must be differentiated from a pseudomyxosarcoma, which develops by mucoid degeneration of connective tissue or cartilage in the tumor.

A fibrosarcomatous area of an osteogenic sarcoma may be poorer or richer in cells (Fig 266). In certain areas, it may resemble dense connective tissue. In other areas, the fibers are few and the cells show a pronounced pleomorphism. Small round cells and spindle cells are mingled with cells in all stages of transition to uninuclear or polynuclear giant cells. These giant cells vary considerably in size and shape and may develop phagocytic properties. Giant cells of a tumor which are filled with erythrocytes are shown in Fig 238. Cartilage in an osteogenic sarcoma forming chondrosarcomatous areas, may have the structure of fairly well-differentiated hyaline cartilage. More often, immature types of

cartilage are formed being characterized by a decrease in the amount of inter cellular substance. This type of cartilage is rich in cells, which are often small The decrease in intercellular substance may finally lead to formation of a tissue in which large polyhedral cells are separated from each other only by thin septa. This type of tissue may be likened to chondroid tissue as it is found in sesamoid bones.



Fig. 277 —Osteogenic sarcoma of the head of the humerus. Dense network of delicate spicules of atypical bone. (Original magnification ×200 reduced to ⅘)

When bone is formed in an osteogenic sarcoma, one is struck by the variability of the histologic picture (Figs. 267 to 270) It is fairly certain that no osteogenic sarcoma produces mature lamellated bone. Any islands of mature bone found in the tumor are invariably remnants of old bone (Fig 271) As ex plained before, the tumor cell itself cannot and does not resorb bone. The growing tumor only stimulates the normal connective tissue to differentiate osteoclasts. The resorption of bone, therefore ceases if the connective tissue separating tumor from bone is destroyed by the growing tumor and the tumor cells are in direct contact with bone.

The immature bone formed in osteogenic sarcomas is only rarely simila- -- normal immature bone Sometimes it looks as if hyalinized connective tissue

been hastily transformed into "bone" by an impregnation of mineral salts (Fig 272) Sometimes, hyalinized, more or less homogenous connective tissue remain for a long time uncalcified as osteoid tissue (Fig 273) In other cases, a delicat network of thin trabeculae of immature bone forms rapidly in the tumor (Fig 274 to 277) In other cases, bone forms almost solid blocks perforated by a net work of vascularized channels (Fig 271)



Fig. 278.—Osteogenic sarcoma of a vertebra. Many cells of the tumor show a striking similarity to osteoblasts They are arranged in cords. (Original magnification ×270 reduced ⅘)

Cartilage as well as connective tissue may calcify without showing any further changes *Precipitated calcium salts, in the shape of fine granules,* are sometimes seen in connective tissue, wide areas looking as if they were sprinkled with mineral salts (Fig 273) These granules may later fuse and form connecting trabeculae, which are sometimes difficult to differentiate from bone. In an osteogenic sarcoma, the gross and microscopic specimens and roentgenograms may differ widely in accordance with the amount of bone formed. If a great amount of dense bone develops, the tumor is sometimes termed sclerosing (osteo-

blastic) sarcoma (Fig 268) being differentiated from the osteoclastic type in which destruction of bone seems to prevail (Fig 243) This distinction is certainly not logical because it stresses a secondary and quantitative rather than a qualitative difference Destruction of bone is, in fact a common activity in all osteogenic sarcomas.

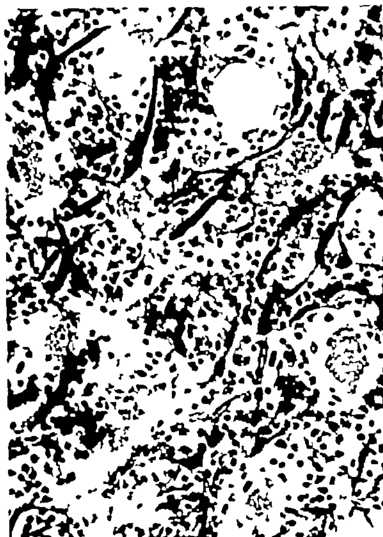


Fig. 279 —Detail from the specimen shown in Fig 278 Spicules of atypical bone have been formed between the osteoblasts. (Original magnification ×480 reduced to)

The cellular elements of some osteogenic sarcomas or better some areas of osteosarcomas show a striking similarity to mature osteoblasts (Fig 278) They are large cells with an eccentric nucleus. The eosinophilic cytoplasm forms a tail on one side of the nucleus (tadpole shape) The cells are densely arranged. In spite of their great number and their mature appearance, they build only a low-grade bone which is laid down in thin trabeculae (Fig 279) Many of these osteoblasts are entirely inactive It is, therefore, questionable whether these cells should be designated as osteoblasts without stressing the

point that the similarity is one of *form* and may be superficial only To term all the cells in a bone-producing osteogenic sarcoma osteoblasts simply because *some of them might differentiate into bone-producing cells is certainly* not justified.

The vascularization of an osteogenic tumor is almost as variable as the structure of the tumor itself Certain tumors are distinguished by an abundance of extremely large thin walled blood vessels and capillaries. Such tumors or tumor areas of this type are sometimes referred to as telangiectatic sarcomas or malignant bone aneurysms. They are characterized by a malignancy higher even than that of the other osteogenic sarcomas because the invasion of the numerous blood vessels by tumor cells seems to occur in an early stage, soon leading to metastases.

Hemorrhage into a tumor or necrosis of part of a tumor may lead to formation of cystic cavities. Necrosis of a tumor may be spontaneous or may be a consequence of irradiation.

In osteogenic sarcoma, metastasis is most often into the lungs because of invasion of the veins by tumor cells. The cells of the tumor may produce cartilage or bone in the metastatic growth similar in all details to the tissue of the primary tumor

TUMORS OF THE ACCESSORY TISSUES OF THE SKELETON

Hemangioma

Any bone of the skeleton may be the site of an hemangioma. The proliferation of blood vessels can start in the periosteum but more often the tumor develops in the bone marrow The tumor consists of great masses of blood vessels which in many hemangiomas, are of an almost even width throughout. Sometimes the vascular spaces are greatly distended and the interstitial connective tissue is compressed to thin septa between the vessels. Because of its similarity to an erectile organ, a hemangioma of this type is termed a cavernous angioma.

A hemangioma may cause extensive destruction of bone which especially in long bones, may be accompanied by compensatory formation of bone leading to a spindly swelling In vertebral bodies, hemangiomas are found rather frequently (Fig 280) One author reported such angiomas in about ten per cent of more than 2 000 autopsies. These tumors had not produced any symptoms. The frequency of occurrence and the seeming stability of such hemangiomas have led to the belief that they are hamartomas that is, congenital malformations rather than true tumors.

In contrast to these vertebral hemangiomas, other cases are known in which the growing tumor destroys or so weakens the vertebral body that a compression fracture results with possible severe injury to the spinal cord. The cavernous hemangioma seems especially to have the potentiality for such destructive growth.

Tumors of the Bone Marrow

Although the rare lipoma and liposarcoma of the skeleton originate in the adipose tissue of the bone marrow, common usage restricts the term tumors



Fig. 210.—Angioma in the body of a vertebra. Accidental finding in a patient with osteomalacia. (Original magnification ×6 reduced to ⅝.)

of the bone marrow to two types of malignant growth, the myeloma and the reticulocytoma. The subdivision of the former and the histogenesis of the latter are still highly controversial. Some clarification might be gained from a consideration of the histology and biology of the normal cellular or hematopoietic marrow in which these tumors originate.

As far as the blood cells are concerned one has to keep in mind that the stem cells of erythrocytes, plasma cells and granulocytes are identical and may have, in the early stages of development, more than one developmental potentiality. This means that from any one of these cells of relatively low differentiation, tumors may arise, the cells of which show some similarity to those of one of the later stages in the development of blood cells. These similarities are in most cases, not identities. If one further considers the possibility that the independently growing and independently differentiating cells of a tumor may also assume a morphologic character which is not represented in any normal tissue the variability of the myeloma can be easily understood. Such terms as erythroblastoma lymphocytoma plasmocytoma, and myelocytoma would better be abolished or should be used with the understanding that the term does not indicate more than a similarity and often a superficial similarity of the tumor cells to certain elements of the bone marrow. The use of the term myelocytoma for all varieties of myeloma is preferred by some authors for the reason that it indicates the common source of the tumor cells. The so-called diffuse myeloma does not seem to be a tumor but rather an aleukemic plasma-cell leukemia.

The second source of tumors of the bone marrow is its supporting tissue that is, the reticular connective tissue, with its characteristic cells, the reticulocytes. Some authors classify tumors of this type as endothelioma others differentiate between reticulocytoma and endothelioma. This classification seems illogical if one thinks of the specialization of the capillaries of the blood forming marrow. They are spaces lined not with typical endothelial cells but with macrophages derived from reticular cells. Because endothelial cells are replaced by macrophages, the capillaries of the bone marrow are often described as open blood sinuses. The fact that the reticular cells of the bone marrow also assume the function of the endothelial cells makes understandable the peculiar affinity of tumors arising from these cells to blood vessels and the fact that these tumors sometimes form the walls of blood-containing channels.

Myeloma.—Myelomas may be found in any bone but are most commonly found in the sternum, the ribs, the vertebrae, and the skull, bones that play the most prominent role in hematopoiesis in the adult. The presence of a large number of foci at the time of the first examination has led to the term multiple myeloma. The multiple occurrence was regarded by many authors as primary and this belief led to the interpretation of the myeloma as a systemic lesion of the hematopoietic tissues and to its separation from true tumors. Other authors maintain that the development of the multiple myeloma begins with the growth of one node, the other nodes being comparable with metastatic tumors. In spite of numerous attempts to answer it, the question of classification of the myeloma is still open.

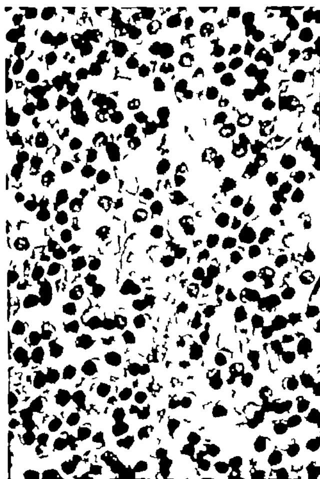


Fig 281 —Multiple myeloma Cells of plasma cell type (Original magnification ×850 reduced t ⅘) (Specimen, courtesy Army Medical Museum)



Fig. 182.—High magnification of a multiple myeloma of plasma cell type. Note the cart wheel structure of the nuclei. (Original magnification X1700 reduced to ⅔.) (Specimen, courtesy Army Medical Museum.)

The cellular character of a myeloma varies considerably, but apparently the nodes of each case are uniform. The foci are generally richly vascularized, their supporting tissue being a delicate framework of reticular fibers. On the basis of cell type the following classification was suggested

1 Myelocytoma with cells similar to myelocytes of the normal bone marrow

2. Erythroblastoma with cells which are said to contain hemoglobin.

3 Lymphocytoma consisting of lymphatic tissue comparable with that found in lymphosarcoma

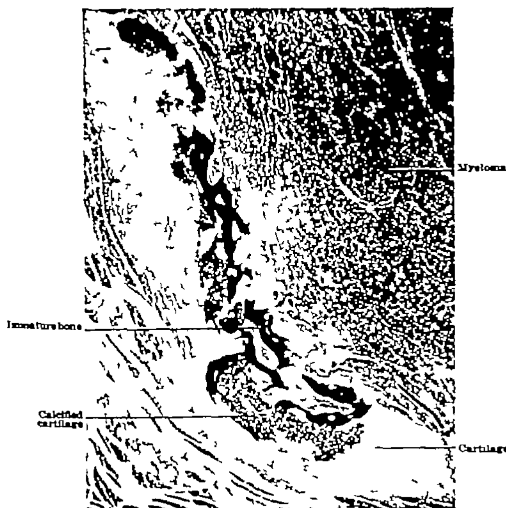


Fig. 283.—Callus formation in the humerus in multiple myeloma. (Original magnification ×10; reduced to ⅔) (Specimen, courtesy Army Medical Museum.)

4. Plasmacytoma, the most frequent type of myeloma, the cells of which show the characteristic cartwheel structure of the eccentric nucleus and the vacuole of the typical plasma cell (Figs. 281 and 282)

The nodes of the myeloma cause considerable destruction of bone tissue which rarely is accompanied by compensatory formation of bone. The nodes

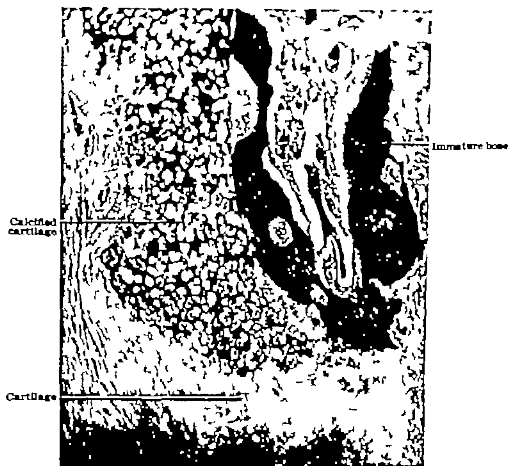


Fig. 284.—Detail of section shown in Fig. 283. Hyaline cartilage, partly calcified, and immature bone (Original magnification ×120 reduced to [illegible].)

appear therefore in roentgenograms as sharply demarcated punched-out defects of the bones. The infrequency of compensatory bone formation explains the relatively common occurrence of pathologic fractures (Figs. 283 and 284)

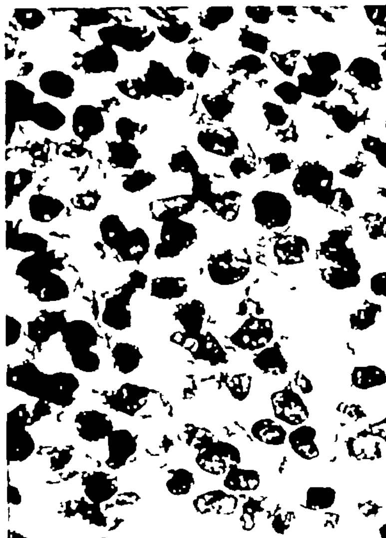


Fig. 285.—Reticulocytoma (Ewing's sarcoma) Cells from a pulmonary metastasis. (Original magnification ×1700 reduced to) (Specimen, courtesy Dr E. Loeffler)

Reticulocytoma.—The reticulocytoma of the bone marrow Ewing's endothelioma, doubtless a true malignant tumor consists of round cells with a large nucleus (Fig 285) The cells are densely packed and supported by a sparse reticular stroma The affinity of these cells to blood vessels can be seen in their arrangement in perivascular cords. The tumor cells themselves may form the walls of blood channels. Angiomatous proliferation of blood vessels is sometimes associated with Ewing's endothelioma (Figs. 286 and 287)

The destruction of bone by a reticulocytoma which can be extensive is generally accompanied by sometimes even excessive compensatory formation of new bone.

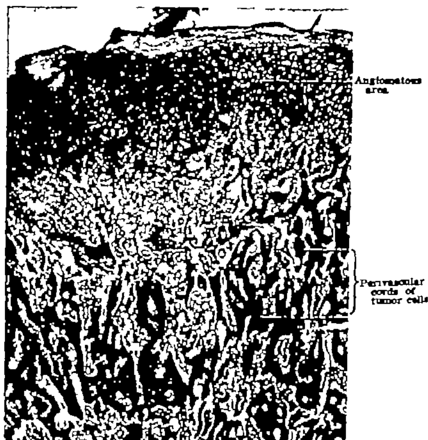


Fig. 186.—Reticulocytoma (Ewing's sarcoma) of the angiomatous type. Angiomatous area and perivascular strands of tumor cells. (Original magnification ×30; reduced to ⅔.) (Specimen, courtesy Army Medical Museum.)



Fig. [illegible] —Blood vessels from the angiomatous reticulocytoma shown in Fig. [illegible]. (Original magnification ×[illegible] reduced to [illegible].)

METASTATIC TUMORS OF THE SKELETON

Metastatic tumors of the skeleton arise rarely from a sarcoma but quite frequently from a carcinoma. Certain types of carcinoma seem to cause skeletal metastasis almost regularly or, at least, more frequently than others. Listed in order of frequency, carcinoma of the prostate and lung hypernephromas, and carcinoma of the breast and thyroid gland cause skeletal metastasis.

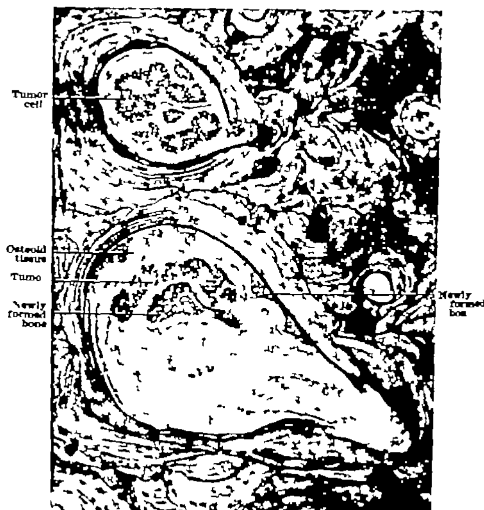


Fig 288 —Osteoblastic metastasi of a carcinoma of the prostate in the mandible. Formation of new immature bone in marrow spaces containing tumor cells. (Original magnification ×125 reduced to ⅘)

Although the reaction of the bone to a metastatic tumor is, in many instances, exactly the same as that to a primary tumor there are a few significant exceptions. Most metastases lead to bone destruction accompanied by compensatory formation of bone. Metastases of mammary carcinoma, in some cases, and metastases of prostate carcinoma (Figs. 288 and 289) frequently lead to excessive formation of new bone and are therefore, termed osteoblastic or osteoplastic metastases in contradistinction to the more common osteoclastic metastases.

The production of new bone under the influence of osteoblastic metastases has to be sharply differentiated from the compensatory formation of new bone which is a characteristic sequence of bone destruction In the metastases of a prostate carcinoma bone destruction is almost entirely absent or insignificant. Occasional bone resorption is possibly caused by vascular disturbances in the involved bone The fact that the cells of the carcinoma invading a bone stimulate the connective tissue in marrow spaces or in Haversian canals to osteoblastic

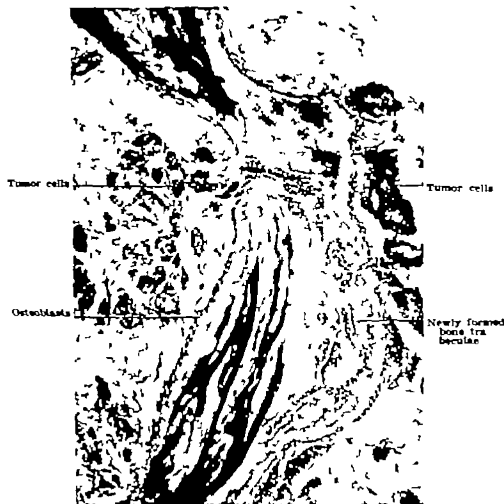


Fig 219.—Same specimen as shown in Fig. 218. Formation of new bone along a trabecula. (Original magnification X125 reduced to ¾)

activity explains the infiltrative growth characteristic for such metastases. Instead of developing to a node of increasing volume, the metastasis of a prostate carcinoma creeps along the Haversian or marrow spaces of a bone slowly infiltrating an entire bone. The formation of a solid node is possible only under progressive destruction of the surrounding bone The cells of a metastasis of a prostate carcinoma, by their stimulating influence on the osteoblasts, erect a barrier of newly formed bone (osteoid tissue) on the walls of the bone space that they in

vade, and their further proliferation cannot lead to an enlargement of this ever narrowing space. Thus the proliferation must follow the connective tissue contained in the vascular and marrow spaces of the bone.

The 'osteoblastic' quality of cells of a prostate carcinoma can be explained only as a metabolic peculiarity of these cells. The high content of phosphatase of these cells may be a decisive factor. This quality of the cells of the prostate gland is reminiscent of a similar quality of other epithelial cells of the urinary tract. As has been mentioned (page 313) transplantation of bladder mucosa into connective tissue induces heterotopic formation of bone.

CHAPTER XI

IDIOPATHIC LESIONS OF THE SKELETON

PAGET'S DISEASE
FIBROUS DYSPLASIA
OSTEOID OSTEOMA
CHMENTOMA

A. PAGET'S DISEASE

Symptoms

Paget's bone disease osteitis deformans must be considered as an isolated pathologic entity because attempts at classifying it either as a tumor or as an inflammatory disease have not been entirely successful In spite of the chaotic variety of the histologic picture there is one common factor namely the enlargement of the involved bones, which always leads to disfiguration of the bone hence, the name osteitis deformans.

The disease which may involve one, a few or many bones develops in the majority of cases after the fortieth year The bones most frequently affected are the sacrum and vertebrae, the femur skull, sternum, and pelvis. Bones which are under special mechanical stress seem to suffer most often. The disease does not spread from one bone to the other across an articulation (Figs. 290 and 291)

Early diagnosis is difficult. Later the symptoms are characteristic: increase in circumference of the skull, curving of certain bones of the extremities, and sometimes spontaneous fractures. In severe cases, a characteristic apelike posture and gait develop

Macroscopically the involved bone is thickened and presents a rough, uneven surface. Long bones often show considerable bending The compact bone is replaced by spongy bone of varying density and the marrow cavity may be narrowed. If the cranium is involved the bones of the vault of the skull are sometimes greatly thickened, mainly by eccentric apposition, without encroaching on the brain. A difference between inner and outer plate and diploë has often disappeared, and the bone in its entire thickness consists of spongiosa (Figs. 292 and 293) The density and arrangement of the diploë vary greatly Areas of sclerosis and porosis are numerous (Figs. 292 and 293) If the base of the skull is involved, it sometimes shows a characteristic deformity bulging far into the cranial cavity with severe damage to the brain as a consequence

The bones of the facial skeleton are less frequently involved than those of the neurocranium. Thickening and deformation of the facial bones lead to a characteristic disfiguration of the face facies leontina The underlying skeletal



Fig 294—Sagittal section through the temporomandibular joint in Paget's disease. The mandible is entirely free of pathologic changes which are highly ad ced in the temporal bone. (Original magnification ×12 reduced to ¾.) (Balint Orban.)

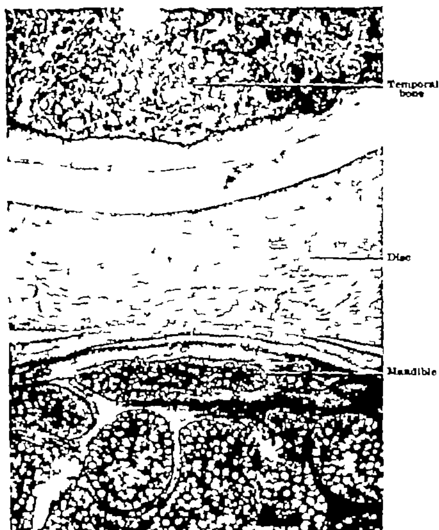


Fig. 291.—Detail of section shown in Fig. 290. (Original magnification ×32 reduced to [illegible]) to [illegible])



Fig. 202.—Section through the generally thickened skull in Paget's disease. Zone of activity along the oute and inner surfaces. In the center a focus of sclerosis in the otherwise porotic zone. (Magnification ×4.)



Fig. 191.—Section through the generally thickened skull in Paget's disease. Outer and inner plates replaced by dense spongy bone. Diploë porotic. (Magnification ×7.)

changes are often referred to as leontiasis ossea, which, however is not a pathologic entity but a symptom of different skeletal changes for example of certain cases of acromegaly and ossifying fibroma.

The bending of long bones and the deformity of the cranial base are described by certain authors as if there were an actual bending or molding of the softened bones. There is no reason to assume that bones in any stage of Paget's disease would consist entirely or mainly of osteoid tissue, which alone would make a mechanical deformation possible. Only a combination of Paget's disease with osteomalacia could account for an actual plasticity of bones. It seems that at least in some cases, the bending of long bones is due to a combination of apposition and resorption This interpretation is supported by observation of a curved and elongated tibia in cases in which the fibula is not involved by Paget's disease and has remained straight. An actual bending can never lead to lengthening of a bone while curving resulting from growth changes necessarily entails elongation.

Histopathology

The histologic changes in Paget's disease are changes of the bone tissue itself and of the bone marrow Briefly the changes in the bone can be characterized as a combination of destruction and repair both of which occur without relation to the statics or the dynamics of the involved bone The result of this oscillating transformation of the bone is always an enlargement of the bone but not always an increase in the volume of bone tissue. The change in the marrow can be summarized as leading through the stage of serous inflammation to fibrosis. This change however is reversible.

The confusing variability of a Paget bone, the coexistence of different stages in closely adjacent areas, is mainly due to the combination of three variable factors. The first is the variable ratio of osteoclastic and osteoblastic activity in a certain area. The second is the variable speed of the destructive and reconstructive processes. *The third is the frequency of local remission of the* pathologic process, followed sooner or later by a resumption of the active changes.

Local differences in the ratio of osteoblastic to osteoclastic activity are responsible for the development of sclerotic and porotic areas, often in closely adjacent areas of the same bone (Fig 294) The resorption by osteoclasts proceeds in attacks which, after a variable time are reversed into periods of bone apposition by osteoblasts, these sequences of destruction and repair being repeated again and again *in the same area. This leads finally to the* development of mosaic bone, one of the characteristic features of Paget's disease (Fig 295) Any part of the bone looks as if it were formed of small pieces fitted together like pieces in a complicated jigsaw puzzle. The lines separating one bony area from the other are mostly reversal lines, rarely resting lines. The lines are wide and stain dark blue in hematoxylin-eosin stained specimens.

An active area is characterized by the presence of numerous osteoclasts and osteoblasts. Sometimes, osteoclasts and rows of osteoblasts alternate on the

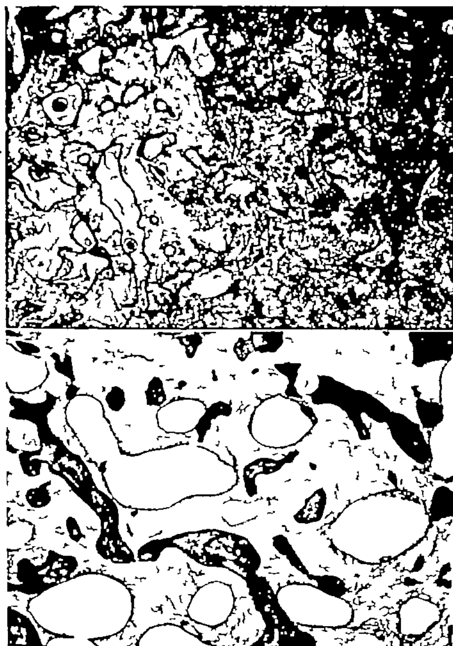


Fig. 204 —Paget disease (Magnification ×22)
A. Advanced sclerosis
B. Porosis with fibrosis of the marrow

surface of one and the same trabecula (Fig 296 *A*) The marrow in such areas is always of the fibrous variety Where osteoblasts are active, the bone trabeculae are often covered by a layer of osteoid tissue of variable thickness

During the time of remission, the bone in a wide area may be aplastic that is, neither osteoclastic resorption nor osteoblastic apposition can be seen. In such areas, the bone marrow may revert to the fatty type (Fig 296 *B*)



Fig 298.—Typical mosaic bone in Paget disease. Note the alteration of areas of immature and areas of mature bone.

Sooner or later the period of inactivity comes to an end and destruction of the resting bone starts again. The early phase of recurrence starts often by tunneling resorption of the bone trabeculae, removing first their central part (Fig 297) Such newly formed marrow spaces are filled with fibrous marrow which replaces the fatty marrow in the zone of renewed activity

The type of bone formed in Paget's disease varies considerably and is probably dependent on the speed of its formation. Thus, we see that, in zones of high activity characterized by a great number of osteoblasts, bone of the immature, coarse fibrillar type is laid down. The degree of immaturity which

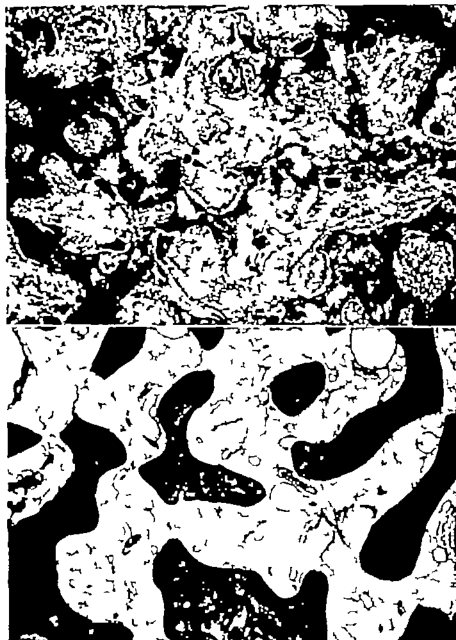


Fig. 236.—Paget disease (Magnification ×32.)

A Highly acti e rea. Not the n mbe of osteoclasts and osteoblasts and the seams of osteoid tissue. The bone is of the immature type. The bon marrow is in the stage of serous inflammation

B Resting area The bone is partly of imm ture, partly of mature type. The marrow is fatty



Fig. 297.—Paget disease. Recurrence of activity after a remission.

A. Osteoclastic and osteoblastic activity in the center and on the surface of some trabeculae which consist partly of lamellated bone. In the zone of activity the marrow is fibrous; in the inactive zone central area of the picture fatty. (Magnification ×32.)

B. Tunneling resorption of bone trabecula in reactivation of the destructive process. The attacked bone is typical mosaic bone, consisting partly of immature, partly of mature bone fragments. Inflammatory edema in the marrow. (Magnification ×40.)

varies, can be determined from the degree of irregularity in arrangement of the osteocytes. The more rapid formation of bone is also responsible for a lag in calcification resulting in formation of a rather wide layer of osteoid tissue. The failure of calcification may also be correlated with the total amount of bone formed in the entire skeleton.



Fig. 291.—Inflammatory edema or serous inflammation of the bone marrow in Paget disease. (Original magnification ×150, reduced to ⅗.)

In periods preceding remission or during remission when bone formation is slow mature lamellated bone is laid down. The irregular appearance of the mosaic bone is due not only to its composition of fragments formed at different times, but also to the differences in the level of differentiation of the fragments. The contrast between pieces of immature bone and of lamellated bone is striking.

Gradual destruction of the premorbid bone leads to replacement of compact bone by spongy bone. Thickening of the bone results from formation of osteophyte-like bone trabeculae on the outer surface of the bone. Whether

this is an attempt to reinforce the weakened bone is questionable, since the changes in Paget's disease seem to be largely independent of mechanical conditions.

The changes in the bone marrow are certainly correlated to the changes in the bone tissue, but it is still controversial whether the medullary changes are primary or secondary. Bones of the skull which contain cellular marrow show



Fig 399.—Detail of section shown in Fig. 398 in high magnification. Note the lymphocytes, macrophages, and some fibroblasts along the fibrinous framework. (Original magnification ×800 reduced to ⅘.)

primary changes in arrangement and size of the blood forming cells. The fibrosis of marrow seems to follow the first destructive bone changes. In long bones, the youngest resorptive spaces are already filled with fibrous marrow.

The fibrosis of the marrow seems to be preceded by a peculiar edema of the marrow interpreted as a serous inflammation. In this stage, wide areas of the marrow consist of a fine network of fibrin in a homogeneous substance

(Fig 298) The cells in such an area are mostly lymphocytes, plasma and macrophages Fibroblasts are few (Fig 299) The blood vessels, are hyperemic and sometimes show signs of stasis, may contain only plasma.

Pathogenesis

Nothing is known of the etiology of Paget s disease The early chan the bone marrow are by certain authors interpreted as an indication infection or at least an irritation. The development of osteogenic sarco Paget s disease suggests an increased proliferative activity of the medullar nective tissue of the bones which, in its ultimate exaggeration leads to : nant growth In view of these facts classification of Paget s disease as an l plastic osteitis may not be entirely unjustified.

B FIBROUS DYSPLASIA

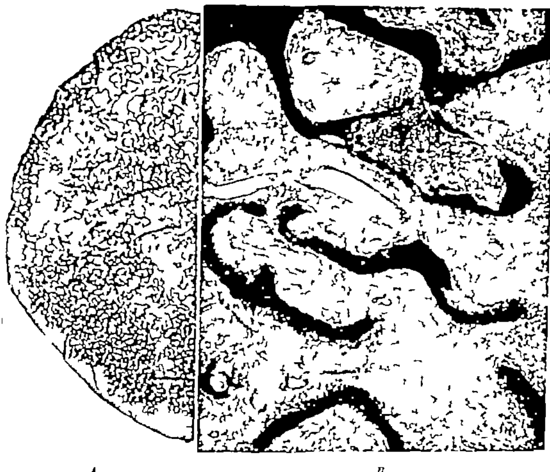
The simultaneous occurrence of peculiar skeletal lesions describ osteitis fibrosa disseminata of endocrine disturbances, mainly hypergon in female patients, and of light brown pigmentation of various skin ar known as Albright s syndrome Soon after the first thorough analysis c disease it was discovered that identical skeletal changes may develop w! any extraskeletal symptoms. These skeletal changes were first describ being polyostotic often, but not always, unilateral. For this disease (skeleton itself the term fibrous dysplasia was coined, and it was reg as a congenital anomaly namely a perverted activity of the specific forming mesenchyme

Some time later the diagnosis fibrous dysplasia was widened to ir also solitary monostotic lesions. Today the fibrous dysplasia has in the of many authors engulfed such discrete disease entities as fibroma, ossi fibroma, and even cysts and giant-cell nodes of the skeleton.

A critical review of the literature and pertinent cases seems to prov facts first, the skeletal disease known as fibrous dysplasia is without dc separate distinct disease entity that in its most severe manifestation, m combined with extraskeletal symptoms second, the single lesion of disease is characterized by a rather stereotyped uniformity The characteristic is one of the valuable symptoms in the differential dia between fibrous dysplasia and other skeletal diseases that show a supe: similarity but present as for instance the ossifying fibroma a great vari the type and the arrangement of the newly formed bone tissue

The etiology of fibrous dysplasia is unknown although the extensi extraskeletal symptoms in severe cases may be a hint to a hitherto covered endocrine basis. The interpretation of the disease as a cong deficiency of the osteogenic tissue is certainly untenable One has to re ber that a specific exclusively osteogenic tissue does not exist The liferating connective tissue that plays the leading role in the developme the skeleton has produced normal bone tissue and bone marrow in a n

For these reasons the term fibrous dysplasia does not seem to be a good choice. As long as the etiology of this disease entity is not known a non prejudicial term for instance osteofibrosis deformans juvenilis (Uehlinger) or polyostotic osteofibromatosis would be preferable



A B

FIG. 390 —Polyostotic fibrous dysplasia a man thirty-seven years old. (Courtesy Dr G A Bennett)

A General view of a typical lesion in the shaft of the fibula. Note the partial replacement of the cortical compacta by spongy bone, and the fairly regular arrangement of thin, curled trabeculae embedded in young fibrous tissue

B High magnification of some of the thin trabecula consisting of immature bone, with signs of resorption and apposition.

The osteofibrosis deformans is a disease of childhood and adolescence It is most frequent between the ages of five and fifteen. The distribution of the foci varies considerably Solitary monostotic lesions are extremely rare Multiple lesions rarely in one bone may involve many bones of both sides or are strictly unilateral The latter type may be restricted to one or may involve both extremities Quite often the scapula humerus radius, and the meta carpal bones of the thumb are affected or again, innominate bone the femur the fibula, and the first metatarsal bone. In the tubular bones diaphyses and metaphyses are the sites of the pathologic changes, while the epiphyses are free or rarely secondarily invaded after the epiph plates have dis-

appeared. Ribs and cranial base are also sites of the disease. Deformities mainly curving and elongation of involved bone have been observed, and also pathologic fractures which have as a rule a good tendency for healing. The disease comes to a standstill at the time of cessation of growth.

Pathogenesis and Histopathology

The lesion starts with the replacement of hemopoietic or fatty marrow by fibrous tissue often resembling in its whorllike arrangement a fibroma. The cortical bone of the diaphysis or the spongy bone of the metaphysis and of flat bones undergoes osteoclastic resorption while the fibrous focus grows. Compensatory periosteal bone formation may take place leading to a swelling of the bone. In the fibrous tissue differentiation of cells into osteoblasts or more rarely into chondroblasts, occurs at an early stage. While the islands of cartilage may degenerate and calcify the newly formed bone seems to manifest a tendency to prolonged growth. Finally a rather regular network of spongy bone occupies the entire focus. The bone trabeculae including fibrous bone marrow always consist of immature coarse fibrillar bone. Often resorption of such trabeculae and formation of new bone can be observed but older foci seem to tend to a relative stability. The loss of compact cortical bone and the presence of the regular network of spongy bone give to a mature focus a characteristic ground glass appearance in the roentgenogram. The foci are as a rule not sharply limited at their proximal and their distal boundaries.

O OSTEOID OSTEOMA

A specific lesion of the skeleton was christened osteoid osteoma though some other terms are being used for the same disease entity for instance corticalis osteoid Bergstrand. The term osteoma implies the nature of the lesion as a tumor but this classification is by no means unequivocal and is not accepted by all investigators.

The lesion is monostotic and, as a rule, affects adolescents or young adults. Sites of predilection are the tibia and femur. Other bones are also affected with *the exception of skull and ribs. In view of the fact that the* osteoid-osteoma has some features in common with the so-called cementoma in the jawbones the lack of lesions diagnosed as osteoid-osteoma in the skull is interesting (see page 457)

The osteoid-osteoma develops either in the spongiosa or the compacta of a bone and has an average diameter of not more than ½ inch. The lesion itself evidently starts as a destructive process, leading to the development of a focus of young highly vascularized connective tissue replacing the resorbed bone. In this tissue sooner or later the differentiation of new bone occurs in the typical sequence of formation of osteoid tissue and its change into bone by its calcification. The fact that calcification is often delayed leads to the presence of rather conspicuous amounts of osteoid tissue hence the name *osteoid-osteoma*.



A



B



C

Fig 101 —Osteoid-osteoma from the subtrochanteric part of th femu of a boy thirteen years of ge (Courtesy Dr G. A. Bennett.)

A Roentgenogram howi g the harp boundaries of the lesion with little signs of peripheral osteosclerosis

B Section through the entire lesion, howing a thin ing of the cortical layer and some sclerotic changes of the surrounding spongiosa. The lesion is separated from the premorbid bone by a layer of young connectiv tissue however in some areas the newly formed bone has fused with the surrounding bone.

C High agnification of a peripheral area of the lesion howing apposition of bone t the border of be premorbi l bone and apposition as well as resorption at the irregular immature bone tr beculae of the lesion.

The newly formed bone is characterized by its low grade of maturity and by its irregular arrangement The trabeculae sometimes form a loose net work sometimes more compact masses At the periphery of the lesion they are often continuous with the remnants of the old bone Marrow tissue between the trabeculae is of the fibrous type As a rule there is conspicuous tissue reaction in the periphery of the focus, especially if the lesion develops in contact with, or within, the cortical compact bone A variably thick mantle of compact bone envelops the focus often leading to a bulging of the affected area to the outside or into the marrow cavity The compact bone consists either of sclerotic spongy bone or of newly formed periosteal and endosteal compact bone

As mentioned before the classification of this peculiar lesion is still controversial. The majority of workers on the subject feel that the lesion should be regarded as a benign tumor of the skeleton. They are aware of course of the facts that make this classification doubtful namely the early limitation of its growth the disproportionate tissue reaction around the lesion, and finally the constant symptom of pain associated with the lesion. Others think of the osteoid-osteoma as an infectious and inflammatory disease for instance as a primarily chronic osteomyelitis Lack of microscopic signs of inflammation with the exception of small foci of lymphocytic infiltration in its neighborhood, and also the persistence of the lesion for a long time without any signs of resolution make this second classification also doubtful Until and unless more cogent observations are available it is almost left to the taste of the author into which group of diseases he wants to count the osteoid-osteoma. Which ever classification is preferred, all authors agree that the lesion is benign. Simple removal of the focus leads to complete healing

D CEMENTOMA

Cementomas are said to develop from foci of loose connective tissue in the jaws, when some of the cells differentiate into cementoblasts. This idea of pathogenesis of the cementoma and the term itself as used today contra dict basic biologic facts. Cementum cannot be recognized as specific tissue per se. Only if the differentiation of cementoblasts is induced by the prox imity of dentin or enamel and only if the resulting hard tissue is laid down upon enamel or dentin, can this modified bone be called cementum. This term implies not only topographical but more important specific biologic qualities. The most important of these are continued growth and lack of the interplay of resorption and rebuilding characteristic for bone For these reasons only a mass of hard tissue continuous with the normal cementum should be called a cementoma. However these latter overgrowths of cementum are generally spoken of as hypercementoses

The first question that arises in an attempt to clarify the pathology of the so-called cementoma is that of the unity of this disease. In all probability there are at least two pathologic entities that have to be differentiated. The first is to be classified as a tumor and more specifically as an ossifying fibroma

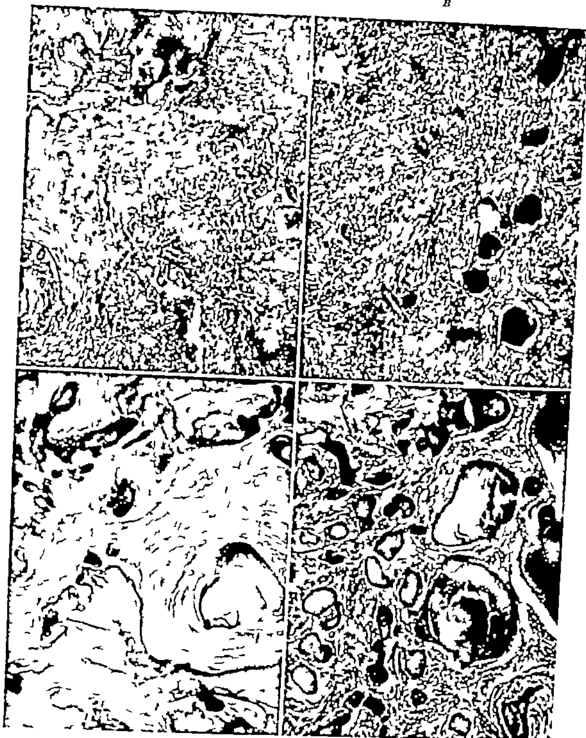


Fig 304.—Light sections through so-called cementomas to show the variability of the newly formed bone

A Irregular trabeculae of immature bone partly uncalcified, formed in young connective tissue (Case No 40, courtesy Dr E. C. Stafne)

B In the proximity of immature trabeculae of bone, irregularly rounded bodies of bone are found, simulating cementicles. (Case No. 40 courtesy Dr E. C. Stafne)

C The newly formed bone is found in the shape of trabeculae as well as of larger masses. In many areas empty lacunae can be seen, while others contain osteocytes. (Case No. 184 51.)

D The fibrous tissue contains irregular bodies of different size, again simulating cementicles. The larger bodies have engulfed smaller ones during their growth. The striated osteoid border in some areas resembles bundle bone or cementum. (Case No. 41 courtesy Dr E. C. Stafne.)

E F

G H

Fig. 302 (Cont'd.)—The growing islands of bone have coalesced into sclerotic spongy bone with fibrous tissue filling the narrow spaces. Many cementing lines prove the alternation of bone apposition and resorption. (Case No. 661 51.)

F Massed blocks of lamellated bone have been formed. The tissue in the marrow spaces is fibrous and rich in cells. (Case No. 278 51.)

G Compact bone of mosaic structure. Most lacunae are empty. The connective tissue is reduced to small areas. (Case No. 664 52.)

H Another example of compact bones with prominent cementing lines. This is a second area of specimen C. (Case No. 184 52.)

It is characterized by its unlimited though slow growth and can lead to visible deformities of the jaw It consists of fibrous tissue in which bonelike hard tissue develops. The latter can show any degree of immaturity and is extremely variable in structure and arrangement. The bone may form a network of variably thick trabeculae or irregularly spherical or ovoid masses separated by connective tissue septa Corresponding to the growth of this tumor areas of resorption and apposition can be recognized. In view of the fact that types of hard tissue identical to any one of the described varieties can be observed in other bone forming neoplasms, the location in the jaws and, therefore the proximity to the teeth are not valid reasons to term this hard tissue cementum or the tumor a cementoma.

The second disease entity generally described as cementoma is of an entirely different character Here we deal with small foci of a diameter rarely reaching 10 mm. that show even after several years of observation, no signs of enlargement These foci often close to the apices of teeth frequently are found to be multiple They are more often found in the lower jaw and are more frequent in females The first stage in their development seems to be a sharply demarcated area of bone destruction. In the second stage the connective tissue replacing the lost bone forms bone of an extremely variable structure and arrangement In this respect they duplicate the different types of hard tissue found in ossifying fibromas. Although some of the newly formed trabeculae may be continuous with the surrounding bone the roentgenogram gives the impression that there is a narrow space separating new and old bone The focus is almost always surrounded by an area of sclerotic bone Since it does not seem reasonable to classify the variable hard tissues as cementum or osteocementum, but rather to view them as atypical bone the term multiple endostosis would be preferable This suggested term would also be noncommittal as to the classification of this disease entity which shows some characteristics of an inflammatory and some of a neoplastic character At the present state of our knowledge its classification as an odontogenic tumor or hamartoma is not justified

It is interesting that the described disease entity has some characteristics in common with the osteoid-osteoma while it differs in other aspects from this lesion. Both lesions develop in a circumscribed area of bone destruction. In both there is a reactive sclerosis of the surrounding bone Neither one has a tendency of unlimited enlargement, and both heal after simple removal however pain so characteristic for the osteoid-osteoma is absent in the so-called cementoma The absence of any subjective symptoms explains the well known fact that cementomas are most often detected in routine examination of teeth and jaws.

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CHAPTER II BONES (pages 47 to 138)

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CHAPTER VI THE INFLUENCE OF VITAMINS ON BONE AND BONES (pages 269 to 295)

Vitamin A

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CHAPTER VII THE EFFECT OF MINERALS ON BONE AND BONES (pages 296 to 308)

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CHAPTER VIII HEALING OF BONES (pages 309 to 337)

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